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UNITED STATES DISTRICT COURT
DISTRICT OF NEVADA

AMARIN PHARMA, INC. and AMARIN PHARMACEUTICALS IRELAND LIMITED,

Plaintiffs,

v.

HIKMA PHARMACEUTICALS USA INC., *et al.*,

Defendants.

CASE NO.: 2:16-cv-02525-MMD-NJK

(Consolidated with 2:16-cv-02562-MMD-NJK)

PLAINTIFFS' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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WO '900	WO 2008/004900 (DX 1525) [Stipulated Prior Art (ECF No. 324 ¶ 63)]
Woodman	Woodman, et al., *Docosahexaenoic acid but not eicosapentaenoic acid increases LDL particle size in treated hypertensive type 2 diabetic patients*, 26 Diabetes Care 253 (2003) (PX 563) [Stipulated Prior Art (ECF No. 324 ¶ 74)]
Yokoyama 2003	Yokoyama et al., *Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS)*, 146 AM. HEART J. 613-20 (2003) (DX 1552) [Stipulated Prior Art (ECF No. 324 ¶ 52)]
Yokoyama 2007	Yokoyama et al., *Effects of Eicosapentaenoic Acido n Major Coronary Events in Hypercholesterolaemic Patients (JELIS): a Randomized Open-Label, Blinded Endpoint Analysis*, 369 LANCET 1090-98 (2007) (DX 1553) [Stipulated Prior Art (ECF No. 324 ¶ 61)]
ZS Associates PhysPulse Findings 2014	ZS Associates Presentation, "Vascepa Wave 2 PhysPulse Findings" (Aug. 2014) (PX 580)

I. INTRODUCTION

1. Vascepa®[1] is a pharmaceutical comprised of a highly purified omega-3 fatty acid called "EPA," administered in a 4 g daily dose. Clinicians prescribe VASCEPA to treat patients with severely elevated triglycerides ("TGs"), a type of fat molecule found in blood. Elevated TGs are associated with an increased risk of cardiovascular events such as heart attack and stroke. However, patients with very high levels of TGs (500 mg/dL or greater), a condition known as severe hypertriglyceridemia, are also at risk of developing pancreatitis, a life-threatening inflammation of the pancreas. So severe is the potential harm from pancreatitis that addressing a patient's severely elevated TGs takes precedence over reducing her risk of cardiovascular events.

2. VASCEPA is a major advance in the treatment of severe hypertriglyceridemia. Prior approved treatments lowered TGs, but dramatically raised LDL-C (the so-called "bad cholesterol")—thereby putting patients at greater risk of cardiovascular disease. VASCEPA met a long-felt need by eliminating this tradeoff, providing for the first time a well-tolerated and effective medication to reduce TGs in persons with severe hypertriglyceridemia without increasing LDL-C. Trial Tr. 851:15–852:1 (Heinecke Cross). And far from increasing cardiovascular risk, VASCEPA has now been shown to dramatically reduce that risk—an achievement that FDA has recognized. *See* PX 1185 (FDA Press Release) at 1 ("VASCEPA is the first FDA approved drug to reduce cardiovascular risk among patients with elevated triglyceride levels as an add-on to maximally tolerated statin therapy."). VASCEPA is the first and only treatment for severe hypertriglyceridemia shown to reduce cardiovascular risk. Trial Tr. 851:19–21 (Heinecke Cross); *id.* at 1122:10–14 (Fisher Cross).

3. Defendants seek to sell generic copies of VASCEPA prior to the expiration of Amarin's patents, which cover methods of treating severe hypertriglyceridemia with purified EPA. Defendants contend that they should be entitled to launch their generic products because allegedly (1) they do not infringe Amarin's patents, and (2) Amarin's patents are invalid as obvious.

[1] The ® symbol will generally be omitted herein.

4. A trial was held in this case from January 13 to January 28, 2020. The evidence established that Amarin's asserted patent claims are infringed and that Defendants have not met their burden to prove obviousness. Judgment should therefore be entered in Amarin's favor.

5. First, the evidence showed that Defendants induce infringement of the Asserted Claims. The Asserted Claims cover methods of treating severely hypertriglyceridemic patients by administering 4 g/day of highly-purified EPA (typically at least 96% EPA and substantially no DHA or other omega-3 fatty acids) for at least 12 weeks, thereby providing physicians with a way to reduce TGs in these patients without increasing LDL-C while also achieving other beneficial effects, such as a reduction in atherogenic apolipoprotein B ("apo B") lipoproteins. The evidence established that through their proposed labeling—which Defendants have copied from VASCEPA's labeling—Defendants will encourage prescribers to carry out the claimed methods, thus inducing infringement.

6. The evidence also refuted Defendants' assertion that the Asserted Claims (*see* ¶ 9) were obvious as of the March 2008 priority date. To succeed in their obviousness attack, Defendants needed to show—by clear and convincing evidence—that the prior art would have motivated a person of ordinary skill in the art to carry out the claimed methods of treating severe hypertriglyceridemia and would have provided a reasonable expectation of success in achieving the claimed results. Yet none of Defendants' cited prior art suggested a benefit in using 4 g purified EPA to treat severe hypertriglyceridemia, or provided a reason to modify Lovaza, (an existing approved treatment for severe hypertriglyceridemia) by eliminating DHA to arrive at the Asserted Claims (*see* ¶ 9), as Defendants alleged.

7. The prior art offered no reasonable expectation that 4 g high purity EPA would avoid large increases in LDL-C in patients with severe hypertriglyceridemia, or achieve other claimed lipid effects such as reductions in apo B. To the contrary, the evidence established that a long-standing belief in the field was that reducing TGs in those patients invariably increased LDL-C, an effect seen in every previously approved treatment. The evidence further established that VASCEPA was the first TG-lowering agent successfully shown (in Amarin's MARINE clinical

trial) to reduce TGs in severely hypertriglyceridemic patients without raising LDL-C—a clinical outcome that defied even the expectations of the outside experts Amarin consulted prior to initiating its clinical program. *See* PX 754 (Expert Panel Notes) at 2 (predicting that with VASCEPA "LDL-C is likely to go up as it does with virtually all [TG] lowering therapies in this group of [severely hypertriglyceridemic] patients").

8. Defendants' obviousness attack was further refuted by numerous objective indicia of non-obviousness—including that the VASCEPA invention met long-felt needs that others had failed to meet in the treatment of severe hypertriglyceridemia, including not just the avoidance of LDL-C increases in reducing TGs but also the significant reduction in cardiovascular risk; that those benefits were both unexpected and met with enthusiastic praise; and that it is, and in the future will continue to be, a commercial success.

II. BACKGROUND OF THE INVENTION

9. In this case, Amarin asserts a total of ten claims from six patents—claims 1 and 16 from U.S. Patent No. 8,293,728 ("the '728 Patent"), Claim 14 from U.S. Patent No. 8,318,715 ("the '715 Patent"), Claims 1 and 8 of the U.S. Patent No. 8,357,677 ("the '677 Patent"), Claim 1 of U.S. Patent No. 8,367,652 ("the '652 Patent"), Claims 4 and 17 of U.S. Patent No. 8,431,560 ("the '560 Patent"), and Claims 1 and 4 of the U.S. Patent No. 8,518,929 ("the '929 Patent") (collectively, the "Asserted Claims"). *See* PX 21 ('728 Patent), PX 22 ('715 Patent), PX 25 ('677 Patent), PX 26 ('653 Patent), PX 30 ('560 Patent), PX 31 ('929 Patent) (collectively, the "Asserted Patents").

10. The Asserted Claims are directed to methods of treating severe hypertriglyceridemia, a condition in which patients' fasting triglyceride levels rise to very high levels of 500 mg/dL or above, by administering 4 grams ("4 g") per day of purified EPA, an omega-3 fatty acid derived from fish oil. Though purified EPA had been approved as a drug product in Japan as far back as 1991, its utility in treating severe hypertriglyceridemia remained unrecognized until the claimed invention here in March 2008. Treating patients with severe hypertriglyceridemia with purified EPA reduced TGs in those patients without increasing LDL-C, the bad-cholesterol.

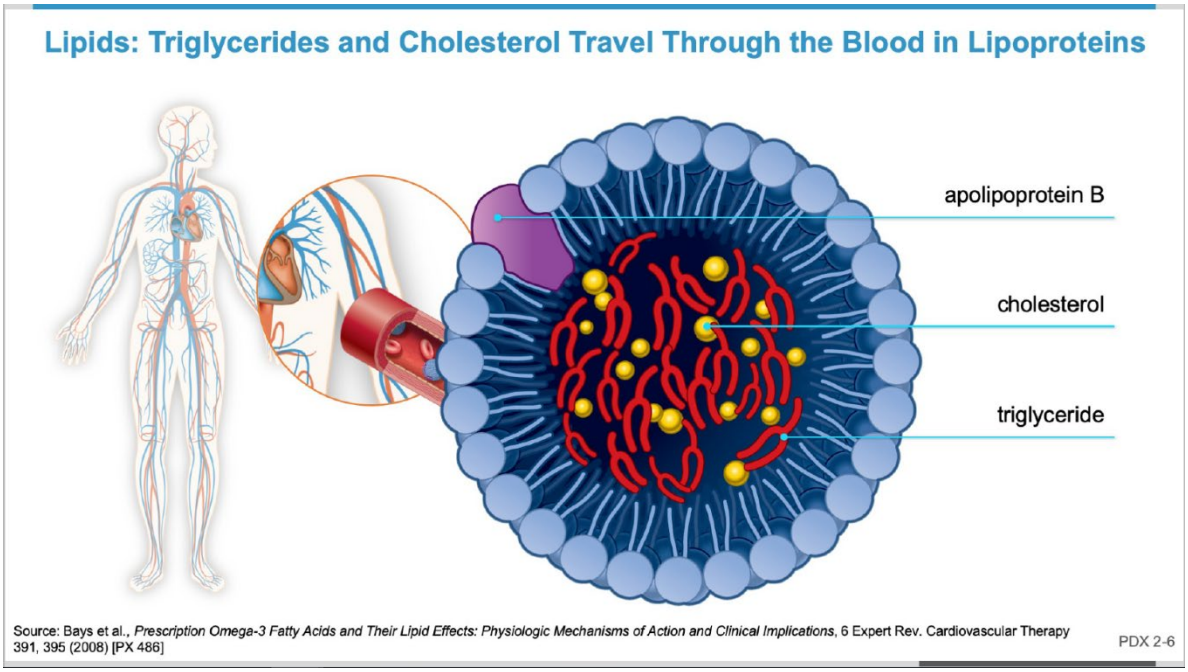
Trial Tr. 851:15–852:1 (Heinecke Cross); Trial Tr. 1574:3–1575:1, 1598:14–17 (Toth Direct). All other treatments for severe hypertriglyceridemia dramatically increased in LDL-C, which then often required to administer of a separate cholesterol-lowering drug, such as a statin, just to address that LDL-C. Trial Tr. 813:8–814:2 (Heinecke Direct); Trial Tr. 1598:18–1599:18 (Toth Direct). Additionally, purified EPA has now been shown to actually reduce cardiovascular risk in severely hypertriglyceridemia patients on top of a statin, the only TG-lowering treatment shown to confer such a benefit. Trial Tr. 849:21–24 (Heinecke Cross); Trial Tr. 1122:6–13 (Fisher Cross); Trial Tr. 1622:5–16; 1625:2–21 (Toth Direct).

11. It is thus clear that administering of 4 grams per day of purified EPA to severely hypertriglyceridemic patients confers unique benefits to patients and is an important addition to the available therapies for the disorder. Defendants concede that the claimed methods of treatment are novel. The sole legal issues presented for decision at trial are infringement and obviousness. To address those issues, it is helpful to review the understanding of severe hypertriglyceridemia and its treatment by a person of ordinary skill in the art in March 2008.

A. Lipids and Lipid Disorders

12. Both TGs and cholesterol are plasma lipids—fatty acid derivatives that circulate through the bloodstream and are delivered to cells to serve biological functions. TGs are a form of energy storage and serve as an energy source for cells. Trial Tr. 1561:21–1562:21 (Toth Direct). Cholesterol, by contrast, is a chemical building block, serving as a precursor for vitamins and hormones. Trial Tr. 324:16–325:5 (Budoff Direct).

13. ***Lipoproteins.*** TGs and cholesterol are not water soluble and so cannot be dissolved directly into plasma (the aqueous part of blood). Trial Tr. 1562:12–17 (Toth Direct). Instead, they are carried through the bloodstream as part of biochemical units called lipoproteins. Trial Tr. 324:5–9 (Budoff Direct); Trial Tr. 1562:12–17 (Toth Direct). This is illustrated in PDX 2-6:

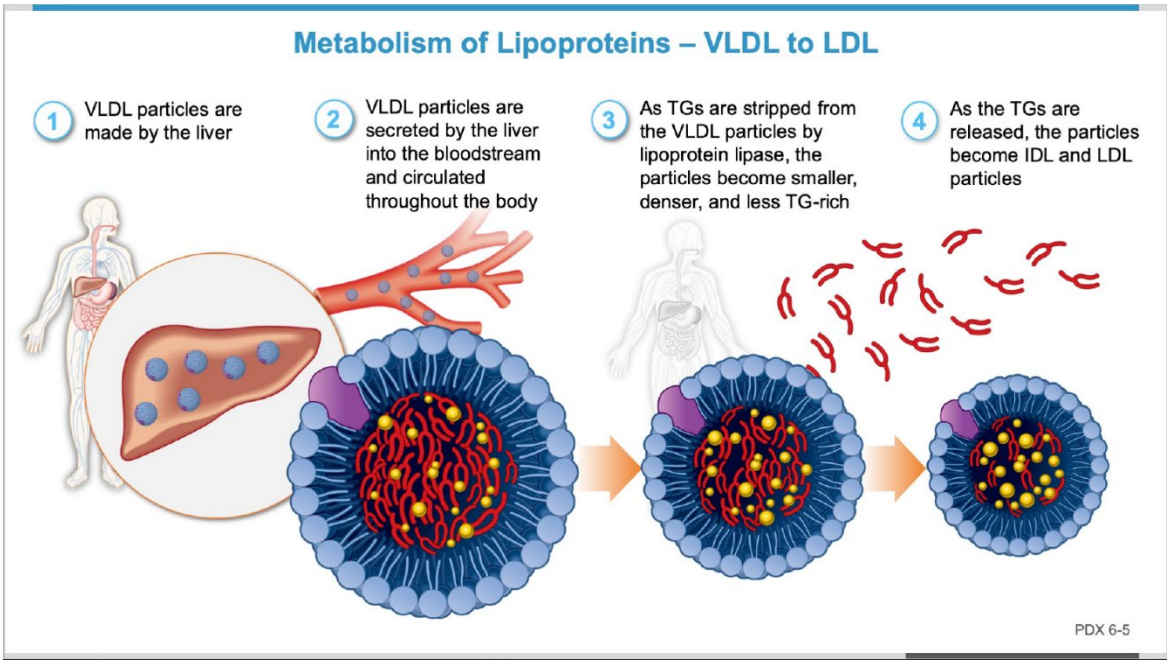


14. Lipoproteins are carriers built on apolipoprotein molecules that surround water-insoluble lipids such as TGs and cholesterol with a surface layer of phospholipids. Trial Tr. 324:6–15 (Budoff Direct) (referring to PDX 2-6).

15. The principal lipoprotein at issue in this case is that containing apo B. Apo B lipoproteins serve the important purpose of carrying TGs and cholesterol through the bloodstream to cells but also, unfortunately, contribute to atherosclerosis. Trial Tr. 325:21–326:12 (Budoff Direct). Each apo B particle contains a single apo B lipoprotein. Trial Tr. 94:2–6 (Ketchum Direct); Trial Tr. 324:5–15; 325:10–17 (Budoff Direct). The apo B lipoprotein evolves as it travels through the blood, becoming smaller and denser as it delivers its TGs and becomes predominantly cholesterol. Trial Tr. 1561:21–1563:25 (Toth Direct).

16. Apo B lipoproteins are classified on the basis of their composition and density. As first produced by the liver, the lipoprotein is a "very low density lipoprotein" (VLDL), rich in triglycerides and a relatively small proportion of cholesterol. Trial Tr. 1562:1–8 (Toth Direct). However, as enzymes, such as lipoprotein lipase, remove the TGs from the lipoprotein, it shrinks in size and becomes denser, with relatively more cholesterol and less TGs. In this process, VLDL is converted to, first, "[i]ntermediate density lipoproteins" (IDL) and then, "low- density

lipoprotein" (LDL). Trial Tr. 1563:2–25 (Toth Direct); Trial Tr. 325:22–326:12 (Budoff Direct). This process is illustrated in the following demonstrative, PDX 6-5, used with Dr. Toth's testimony:



17. This mechanism by which VLDL lipoproteins were converted to IDL and LDL was well understood by a person of ordinary skill as of March 2008. Trial Tr. 1566:1–3 (Toth Direct).

18. Although all apo B particles are thought to contribute to atherosclerosis, it is LDL and its associated cholesterol, termed LDL-C, that is most associated with adverse cardiovascular events such as heart attacks and strokes. Trial Tr. 94:4–6 (Ketchum Direct); Trial Tr. 324:5–15; 325:10–17 (Budoff Direct); *see also* PX 989 (ATP-III) at 22; DX 1876 (ATP-III) at 19[2] (describing LDL as the "most abundant and clearly evident atherogenic" of the lipoproteins and observing that LDL-C, the cholesterol in LDL-particles, made the greatest contribution to the development of atherosclerosis).

19. Two other lipoproteins are chylomicrons, which carry the lipids from the intestines after a meal, and high-density lipoproteins ("HDL"), the so-called good cholesterol particle, which

[2] Exhibits PX 989 and DX 1876 both refer to ATP-III. Because the pagination of PX 989 and DX 1876 differs, parallel cites to ATP-III are provided herein.

helps to remove cholesterol. Trial Tr. 1645:23–1646:2, 1680:12–21 (Toth Direct); PX 486 (Bays 2008 I) at 3.

B. Severe Hypertriglyceridemia

20. When TG levels in the blood become abnormally high, the result is a disorder known as hypertriglyceridemia. *See* PX 989 (ATP-III) at 190; DX 1876 (ATP-III) at 177. If TGs are very high (≥ 500 mg/dL), the condition is known as severe hypertriglyceridemia. Trial Tr. 1566:4–16 (Toth Direct); PX 989 (ATP-III) at 190; DX 1876 (ATP-III) at 177.

21. Clinicians treating patients have long recognized the existence of different classes of hypertriglyceridemia based on a patient's baseline fasting TG levels. At the time of the invention in March 2008, this recognition was reflected in ATP-III, an authoritative source for treating lipid disorders. *See, e.g.*, Trial Tr. 328:17–23 (Budoff Direct) (describing ATP-III as "a very widely used and established guideline in the field"); Trial Tr. 1122:5 (Fisher Cross) (describing ATP-III as "the ruling guidelines" in 2008); Trial Tr. 839:9–21 (Heinecke Cross) (describing that the ATP-III definition of severe hypertriglyceridemia is used by FDA). ATP-III divided hypertriglyceridemic patients into three classes based on the fasting TG levels in their blood—(1) borderline-high (150–199 mg/dL); (2) high (200–499 mg/dL); and (3) very high TGs (≥ 500 mg/dL). PX 989 (ATP-III) at 190, 194; DX 1876 (ATP-III) at 177, 181. As of March 2008, these classifications were well accepted, and are still recognized today. Trial Tr. 1568:1–1569:24 (Toth Direct).

1. Causes of Severe Hypertriglyceridemia

22. Severe hypertriglyceridemia is primarily a genetic disorder. Trial Tr. 332:4–7 (Budoff Direct) ("So hypertriglyceridemia is primarily a genetic disorder, so we're born with it. We don't have – we don't process – we don't have certain enzymes, or we have deficiencies in certain enzymes."); Trial Tr. 333:17–20 (Budoff Direct) ("Genetic[s] . . . that's the largest and most common cause of very high triglyceride[s]"); Trial Tr. 461:8–11 (Budoff Cross) ("Q. And most commonly, severe hypertriglyceridemia is caused by unhealthy diet and poor lifestyle choices, right? A. No, most commonly it's caused by genetics."); PX 289 (VASCEPA FDA

Medical Review) at 41 ("Patients with very high TG have a strong genetic component to their disease[.]"); PX 269 (Miller 2011) at 12 Tbl. 5 (listing "Genetic" as the first cause of severe hypertriglyceridemia); PX 925 (McKenney II) at 2, ("The higher the triglyceride level, the more likely genetics play a role. For example, triglyceride levels above 500 mg/dL are often seen in patients with familial hypertriglyceridemia[.]"); *see* PX 288 (Karalis) at 10 ("[C]onsideration may be given to discontinuing the non-statin lowering medication [EPA.] However the TG levels will need to be monitored closely for any rise in the TG levels."); Trial Tr. 374:2–380:16 (Budoff Direct) (discussing the Karalis article, explaining that TG levels might rise again because of the genetic nature of the condition)

23. As of March 2008, it had long been understood that genetic impairments relating to lipoprotein lipase was a primary cause of severe hypertriglyceridemia. PX 989 (ATP-III) at 190 Tbl. VII.2-1; DX 1876 (ATP-III) at 177 Tbl. VII.2-1; Trial Tr. 1571:19–1573:25 (Toth Direct). When lipoprotein lipase enzyme activity is impaired, TGs cannot effectively be extracted from VLDL particles—meaning that these TG-rich particles buildup in the blood (like a "logjam"), resulting in very high TGs levels in the blood. Trial Tr. at 1564:6–20, 1583:19–25 (Toth Direct); *see also* PX 486 (Bays 2008) at 3 ("[S]evere hypertriglyceridemia occurs with increased chylomicrons, VLDL particles and/or their remnants, with causality and promotion being due to primary and secondary factors. Primary causes include genetic defects . . . .").

24. As a primarily genetic disorder, severe hypertriglyceridemia is a chronic condition, often requiring long-term (or even life-long) treatment. Trial Tr. 334:4–6 (Budoff Direct) ("[G]enetic causes are lifelong, we're born with them, they stay with us forever and require long-term therapy"); Trial Tr. 354:7–15 (Budoff Direct) ("[O]nce I've already eliminated the short-term causes . . . I then institute [VASCEPA], and I institute VASCEPA for life, because the only people left are people with genetic abnormalities that cause permanent elevations in their triglycerides. So it's always a lifetime treatment."); *see also* Trial Tr. 448:12–449:13 (Budoff Cross); PX 289 (VASCEPA FDA Medical Review) at 142 (FDA identifying VASCEPA as a "chronically

administered drug" by checking the "yes" box for a content parameter only applicable to chronically administered drugs); Trial Tr. 105:11–108:14 (Ketchum Direct).

25. Other contributing factors, or secondary causes, of severe hypertriglyceridemia include metabolism disorders, medications, unhealthy diet and lifestyle, and certain diseases. PX 269 (Miller 2011) at 12. Clinicians sometimes called these "reversible" or "transient" causes of severe hypertriglyceridemia. *See, e.g.*, Trial Tr. 339:9–11 (Budoff Direct); Trial Tr. 369:17–21 (Budoff Direct); Trial Tr. 449:9–13 (Budoff Cross). In other words, patients who experience severe hypertriglyceridemia caused solely by one of these factors do not suffer from a chronic condition. Trial Tr. 449:9–13 (Budoff Cross) ("I described the reversible causes earlier, diabetes out of control, binge drinking, hypothyroidism, as other causes that can push people up into the severe hypertriglyceridemic range that would not be considered a chronic condition.").

26. But, in contrast to patients with borderline (TGs 150–199 mg/dL) or high (TGs 200–499 mg/dL) TG levels, it is unusual for severe hypertriglyceridemia to be caused solely by diet and lifestyle factors. Trial Tr. 338:17–339:2 (Budoff Direct) ("Q. So in your years of treating patients with lipid disorders, how often would you say that you see a patient who has very high triglycerides solely because of diet? A. Yeah so that would be extremely rare . . . I've not seen a three or four-fold reduction in triglycerides just by improving diet."); Trial Tr. 338:9–15 (Budoff Direct) ("[I]f we were to do blood draws of most of the people who are eating too much and drinking too much at any given moment, very, very few of them would have severe hypertriglyceridemia. This is not a common cause of severe hypertriglyceridemia, and, certainly, if you don't have an underlying problem, you don't get to that level."). And even for motivated patients, where poor lifestyle choices are contributing to their severe hypertriglyceridemia, it will often take six months or more for that patient to lose enough weight to be able to get off of TG-lowering medication. Trial Tr. 1175:2–10 (Fisher Cross).

2. Clinical Consequences of Severe Hypertriglyceridemia

27. Patients with severe hypertriglyceridemia face two principal health concerns. Trial Tr. 1567:2–25 (Toth Direct). The first, and most urgent, is a heightened risk of acute pancreatitis.

See PX 989 (ATP-III) at 190, 194; DX 1876 (ATP-III) at 177, 181; Trial Tr. 1569:17–1570:19 (Toth Direct). Pancreatitis, which involves the inflammation of the pancreas, is an excruciatingly painful and potentially life-threatening condition. Trial Tr. 1567:2–22 (Toth Direct) ("In the setting of severe hypertriglyceridemia, inflammatory changes [c]an occur within the pancreas that can lead to sudden devastating injury to the pancreas leading to dissolution of pancreatic tissue, resulting in severe pain, inability to eat, to drink, and it constitutes a medical emergency. But even more importantly[,] in some cases[,] it [can] even result in death."); *see also* Trial Tr. 331:3–20 (Budoff Direct); Trial Tr. 72:4–13 (Ketchum Direct).

28. Patients with severe hypertriglyceridemia are also at increased cardiovascular risk. Trial Tr. 1567:2–25 (Toth Direct); Trial Tr. 840:13–17; PX 989 (ATP-III) at 179; DX 1876 (ATP-III) at 167. Having elevated TG levels has long been known as a risk factor for cardiovascular disease. Trial Tr. 1729:10–1730:5 (Toth Direct). Moreover, many patients with severe hypertriglyceridemia have diabetes, another risk factor for cardiovascular disease. Trial Tr. 1648:3–23 (Toth Direct); Trial Tr. 840:9–17 (Heinecke Cross).

29. The recognition in March 2008 that persons with very high TGs were a special population with distinct treatment needs was reflected in FDA's regulatory review process, which recognized a discrete indication for patients having TG levels of at least 500 mg/dL in the Lovaza product. *See* DX 1535 (Lovaza PDR) at 3.

C. Treatment of Severe Hypertriglyceridemia

1. Goals of Therapy

30. As noted above, the first priority in treating severe hypertriglyceridemia is to reduce the risk of pancreatitis. Thus, the primary goal of therapy, as both sides' experts agreed, is to get a patient's triglyceride levels below 500 mg/dL and to maintain them at that level. *See, e.g*, Trial Tr. 537:6–9 (Budoff Re-Direct) ("Q. What is the therapeutic goal for a patient with severe hypertriglyceridemia? A. The goals and guidelines are to reduce and maintain their triglycerides below 500 milligrams per deciliter."); *id.* at 672:20–25 (Sheinberg Cross) ("standard practice" is "to both reduce and maintain triglyceride levels"); Trial Tr. 1174:4–7 (Fisher Cross) ("[I]n treating

severe hypertriglyceridemia, the goal is to keep the patients below 500 milligrams per deciliter"). The cornerstone of treating hypertriglyceridemia is lifestyle counseling (diet and exercise). Trial Tr. 1170:14–19 (Fisher Cross). However, "TG lowering drugs are usually required in persons with very high TG to prevent acute pancreatitis." PX 289 (VASCEPA FDA Medical Review) at 11; PX 989 (ATP-III) at 195; DX 1876 (ATP-III) at 182 ("Triglyceride lowering drugs (fibrates or nicotinic acid) are usually required and are efficacious in persons with very high triglycerides").

31. So serious is the harm from pancreatitis that reducing triglycerides below 500 mg/dL takes precedence over addressing cardiovascular risk. Trial Tr. 331:16–24 (Budoff Direct). Thus, many physicians treat severely hypertriglyceridemic patients in step-wise fashion: first—after instituting diet and lifestyle improvements—reducing TGs using a TG-lowering agent and then, as a second step—once TGs are brought below 500 mg/dL—adding a statin or other cholesterol-lowering drug to address cardiovascular risk. Trial Tr. 375:12–376:13 (Budoff Direct). For example, 2017 treatment guidelines published in 2017 by Dr. Dean Karalis, which was cited by both sides, advised that "once the TG are lowered[,] consideration should be given to adding a statin to [the patient's] TG-lowering therapy." PX 288 (Karalis) at 10.

32. As the foregoing makes clear, TG-lowering therapy is not stopped when severely hypertriglyceridemic patients' TGs are brought under 500 mg/dL. Trial Tr. 375:6–24 (Budoff Direct) ("So it's not saying stop step one and start over, it's saying you've already put them on [VASCEPA], should I add a statin to further reduce their cardiovascular risk."). Instead, consistent with the treatment goal of maintaining TG levels below 500 mg/dL, patients remain on their TG-lowering medication to ensure that the TG reductions are maintained at that level. Trial Tr. 1174:16–1175:1 (Fisher Cross). The guidelines only recommend discontinuing TG-lowering medication if TGs are reduced to near normal levels, PX 288 (Karalis) at 10, but in practice such reductions are seldom achieved, PX 289 (VASCEPA FDA Medical Review) at 41 ("Therapy is considered successful if TG is lowered to <500 mg/dL; often it is not possible to normalize TG in these patients."); Trial Tr. 378:1–22 (Budoff Direct). As a result, most severely

hypertriglyceridemic patients remain on TG-lowering medication long-term. *See* Trial Tr. 381:22–382:17 (Budoff Direct).

2. The Available Treatments for Severe Hypertriglyceridemia Prior to VASCEPA

33. At the time of the invention, FDA-approved drugs for lowering TGs in patients with severe hypertriglyceridemia included (1) niacin, (2) fibrates, and (3) the omega-3 fatty acid medication Lovaza, also known as Omacor. Trial Tr. 1574:3–7 (Toth Direct); Trial Tr. 340:12–17 (Budoff Direct); Trial Tr. 79:17–25 (Ketchum Direct). Niacin, or nicotinic acid, had been used for decades to treat dyslipidemia. Trial Tr. 1574:22–1576:15 (Toth Direct); PX 1026 (Carlson) at 1. Fibrate products, including Lopid (gemfibrozil) and Tricor (fenofibrate) had also been approved to treat patients with severe hypertriglyceridemia. *See* PX 964 ("Lopid PDR 1990") at 2–3; PX 388 (Tricor Label). And FDA had approved Lovaza, which was a mixture of omega-3 fatty acid ethyl esters, of which the principal components are approximately 465 mg EPA and 375 mg DHA in ethyl ester form. *See* DX 1535 (Lovaza PDR) at 2; PX 566/DX 1578 (Lovaza 2007 Label) at 1.

34. It is undisputed that all of these existing treatment shared a common, significant downside: the reduction in TGs was accompanied by a corresponding large increase in LDL-C. Trial Tr. 1574:1–1598:17 (Toth Direct); Trial Tr. 851:15–852:1 (Heinecke Cross); Trial Tr. 80:15–19 (Ketchum Direct). This meant that severely hypertriglyceridemic patients' pancreatitis risk could only be addressed at the expense of cardiovascular health. Trial Tr. 1577:13–1578:11 (Toth Direct) (explaining that rises in LDL-C increase cardiovascular risk). Moreover, in general, the cardiovascular health of patients with severe hypertriglyceridemia was ignored by the medical community—overshadowed and obscured by the more pressing risk of pancreatitis. Trial Tr. 1121:18–1122:14 (Fisher Cross).

35. While all of the available treatments for severe hypertriglyceridemia were associated with a dramatic rise in LDL-C, these treatments had other drawbacks as well.

36. Niacin had terrible side effects, including that it induced pruritus and head to toe flushing, making the patient look red and creating a very intense sensation of heat, itching, and

tingling. Trial Tr. 1599:25–1600:20 (Toth Direct); Trial Tr. 80:15–19 (Ketchum Direct). In addition, niacin "reduces insulin sensitivity, and higher doses (>3 g/day) often worsen hyperglycemia in persons with type 2 diabetes." PX 989 (ATP-III) at 173, 175; DX 1876 (ATP-III) at 161, 163. This was a problem because many individuals with severe hypertriglyceridemia are diabetic. Trial Tr. 1648:3–23 (Toth Direct).

37. Fibrates also raised safety concerns when co-administered with statins, and could cause rhabdomyolysis—the wasting away of muscle that can lead to kidney failure. Trial Tr. 1602:25–1604:5 (Toth Direct); *see also* PX 923 (McKenney) at 10 ("[F]ibrates can cause myopathy and rhabdomyolysis and should be used with caution in individuals at a high risk of these problems."); Trial Tr. 80:11–14 (Ketchum Direct).

38. Lovaza, too had, additional limitations: some patients experienced eructation, or fishy burps, DX 1535 (Lovaza PDR) at 3, and gastrointestinal problems. Trial Tr. 80:5–10 (Ketchum Direct).

3. A Perceived "General Phenomenon": LDL-C Increases When TGs Are Reduced In Severely Hypertriglyceridemic Patients

39. As noted above, prior to VASCEPA, therapy to reduce TGs in severely hypertriglyceridemic patients was invariably accompanied by large and undesirable increases in LDL-C. Trial Tr. 1574:1–1597:13 (Toth Direct). Indeed, VASCEPA remains unique in this regard. Defendants' expert, Dr. Heinecke, conceded that, of all the drugs approved by FDA to treat severe hypertriglyceridemia, "the only one of those drugs that has been shown that it can be administered to very high triglyceride[] patients to reduce triglycerides without raising LDL-C is [VASCEPA]." Trial Tr. 851:15–852:1 (Heinecke Cross).

40. The rise in LDL-C accompanying treatment of severe hypertriglyceridemia was long recognized as a matter of clinical concern. As ATP-III warns, severe hypertriglyceridemia is associated with metabolic syndrome, type 2 diabetes, and coronary heart disease, all of which increase the risk of adverse cardiovascular events. PX 989 (ATP-III) at 192 Tbl. VII.2-2 DX 1876 (ATP-III) at 179. Increases in LDL-C, which are closely associated with enhanced cardiovascular

risk, would thus be particularly undesirable in such patients. Trial Tr. 1577:22-25 (Toth Direct). Indeed, as far back as 1977, the literature studying the treatment of severe hypertriglyceridemia described the rise in LDL-C as a **"major clinical concern**," noting that the rise "may be quite atherogenic." PX 1026 (Carlson) at 7 (emphasis in original).[3] And even as late as 2011, FDA referred to the increase in LDL-C associated with the prior omega-3 fatty acid product Lovaza as one of the "important safety issues" in its review of VASCEPA for the treatment of severe hypertriglyceridemia. PX 289 (VASCEPA FDA Medical Review) at 14.

41. Despite this concern, all the drugs approved for treatment of severe hypertriglyceridemia over the next thirty years—including niacin, Tricor (fenofibrate), and Lovaza (omega-3-fatty acid esters)—were associated with large increases in LDL-C in patients with very high TGs. *See* PX 1026 (Carlson) at 7 (niacin); PX 388 (Tricor label) at 7 (fenofibrate); DX 1535 (Lovaza PDR) at 3, Tbl. 2 (omega-3 fatty acids); Trial Tr. 1574:1–1597:13 (Toth Direct); Trial Tr. 851:13–852:1 (Heinecke Cross). Compared to placebo, for example, Tricor (fenofibrate) increased LDL-C levels in patients with severe hypertriglyceridemia by 49.2%, while Lovaza increased LDL-C levels by 49.3% in patients with severe hypertriglyceridemia. PX 388 (Tricor Label) at 7, Tbl. 2; DX 1535 (Lovaza PDR) at 3, Tbl. 2; Trial Tr. 1582:11–1583:7, 1589:17–1590:6 (Toth Direct).

42. The rise in LDL-C associated with treating severely hypertriglyceridemic patients was understood to be a "general phenomenon"—a direct consequence of reducing TGs in patients with severe hypertriglyceridemia. PX 1026 (Carlson) at 3; Trial Tr. 1590:12–1591:14 (Toth Direct). This understanding was based not only on the large increases in LDL-C observed with TG-lowering medications in patients with severe hypertriglyceridemia, but also on the mechanism

[3] The Carlson reference refers to patients as having "Type V hyperlipoproteinaemia." It is undisputed that this term is an older term for severe hypertriglyceridemia. Trial Tr. 855:8–15 (Heinecke Cross); *see also* PX 989 (ATP III) at 190; DX 1876 (ATP-III) at 177 ("High triglycerides equate to the older definition of type 4 hyperproteinemia, whereas very high triglycerides were called type 5 hyperproteinemia.").

through which these drugs were understood to work to lower TGs. Trial Tr. 1590:12–1597:13 (Toth Direct).

43. As noted above, severe hypertriglyceridemia had long been understood to have a "strong genetic component," typically associated with impairment of lipoprotein lipase, the enzyme responsible for clearing TGs and converting the large VLDL—the lipoprotein responsible for carrying TGs—to smaller LDL particles. PX 989 (ATP-III) at 190 Tbl. VII.2-1; DX 1876 (ATP-III) at 177 Tbl. VII.2-1; Trial Tr. 1561:16–1566:3, 1571:16–1573:25 (Toth Direct). When lipoprotein lipase enzyme activity is impaired, TGs cannot effectively be extracted from VLDL particles—meaning that these TG-rich VLDL particles buildup in the blood like a "logjam," resulting in a large excess of VLDL particles and high TGs levels in the blood. Trial Tr. 1561:16–1564:22 (Toth Direct).

44. As of March 2008, it was understood that TG-lowering treatments lowered TGs in patients with severe hypertriglyceridemia by helping these patients to convert the large volume of VLDL particles to LDL particles—thus breaking the "logjam" of TG-rich VLDL particles, and thereby lowering TGs levels. Trial Tr. 1590:12–1597:13 (Toth Direct). But the increased conversion of VLDL to LDL meant that as VLDL levels decreased, LDL levels dramatically increased—producing a spike in LDL-C. *Id.*

45. This understanding was reflected in the prior art as of March 2008. For example, the McKenney reference observed that, under the influence of omega-3 fatty acids, "the conversion of VLDL to LDL particles increased 93 percent," and went on to observe that this explained the rise in LDL-C in patients with severe hypertriglyceridemia:

> These results illustrate that the enhanced catabolism of triglycerides produced by P-O3FA results in less secretion and more rapid removal of VLDL particles. *The results also show that VLDL particles are rapidly converted to LDL particles, thus explaining why LDL cholesterol levels may rise in patients with very high triglycerides when given P-O3FA therapy*.

PX 923 (McKenney I) at 5 (emphasis added); *see also* Trial Tr. 1591:12–1595:3 (Toth Direct).

46. Other references echoed this understanding. For example, a reference by Bays entitled *Prescription Omega-3 Fatty Acids* explained that

> As with fibrates, the degree of LDL-C elevations observed with omega-3 treatment is generally related to the pretreatment triglyceride levels. Omega-3 fatty acids increase LDL cholesterol levels the most in patients with the highest pretreatment triglyceride levels. *The reason for the increased LDL cholesterol levels with omega-3 fatty acids is related to the increased conversion of VLDL particles to LDL particles*."

PX 486 (Bays 2008) at 10, 12 (emphasis added); *see also* Trial Tr. 1596:11–1597:13 (Toth Direct).

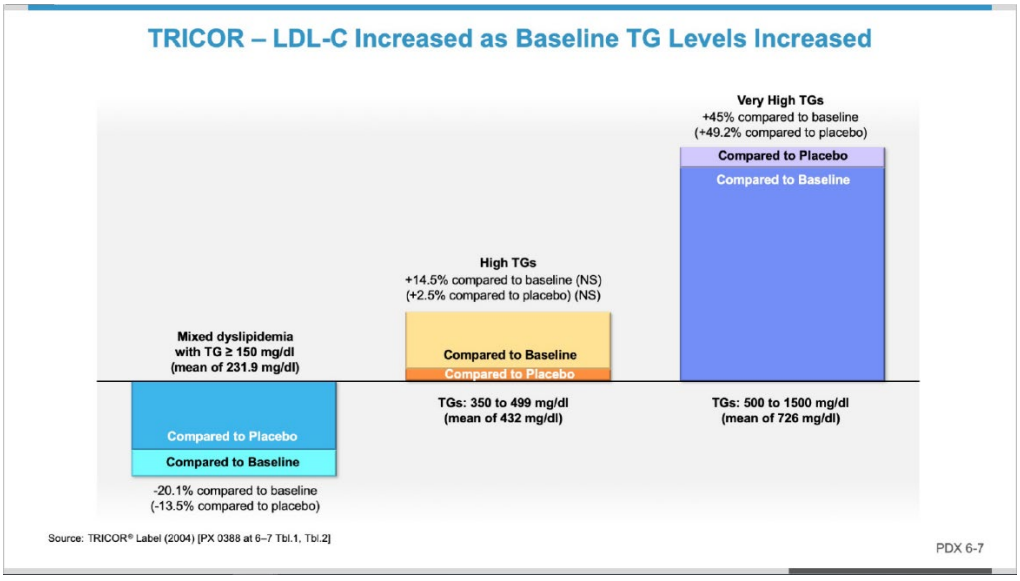
47. Even after 2008, moreover, the understanding continued to be that TG-lowering agents worked to lower TGs in the severely hypertriglyceridemic population by increasing lipoprotein lipase activity, thereby increasing the conversion of VLDL to LDL and, in the process, raising LDL-C. For example, the VASCEPA Medical Review from 2011 reflected FDA's understanding that Lovaza's mechanism for lowering TGs was enhanced conversion of VLDL to LDL—and that this explained the large increase in LDL-C observed with Lovaza in patients with severe hypertriglyceridemia. PX 289 (VASCEPA FDA Medical Review) at 14 ("The increase in LDL-C [with Lovaza] is thought to be due to the increased activity of LPL [lipoprotein lipase] activity. This increased activity enhances the conversion of very low density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) to LDL-C."); Trial Tr. 860:15–863:18 (Heinecke Cross).

48. The understanding that the increased LDL-C in patients with severe hypertriglyceridemia was inherent in the process of lowering their TGs—and was not a side effect of the particular medication—was confirmed by the fact that an increase in LDL-C was also seen with *non-drug therapy* for severe hypertriglyceridemia. For example, the prior art noted that a rise in LDL-C in patients with severe hypertriglyceridemia resulted from a low-fat diet, PX 1026 (Carlson) at 3, as well as exercise-induced weight loss. *See* PX 486 (Bays 2008) at 12.

49. This understanding was further confirmed by the fact that even drugs that either lowered, or did not significantly raise, LDL-C in other lipid disorders characterized by lower levels

of elevated TGs, such as mixed dyslipidemia or hypertriglyceridemia, nonetheless dramatically raised LDL-C in patients with severe hypertriglyceridemia.

50. For example, the TG-lowering agent fenofibrate (marketed under the brand name Tricor) actually *reduced* LDL-C in mixed dyslipidemic patients with merely elevated TGs. PX 388 (Tricor Label) at 6, Tbl. 1 (reporting a 14.5% reduction in LDL-C in patients with mean TG levels of 231.9 mg/dL as compared to placebo); PDX 6-7. Even in patients with high triglycerides—with baseline TGs between 350–499 mg/dL—fenofibrate only increased LDL-C a non-statistically significant ***2.5%*** compared to placebo. PX 388 (Tricor Label) at 7 tbl. 2; PDX 6-7. But when fenofibrate was used to treat severely hypertriglyceridemic patients—those with TGs of at least 500 mg/dL—LDL-C levels increased ***49.2%*** over placebo. PX 388 (Tricor Label;) at 7, Tbl. 2; PDX 6-7; *see also* Trial Tr. 1582:11–1584:19 (Toth Direct). These results, showing the differential effects of fenofibrate in patients with different baseline TG levels (moderately elevated, high, very high, are summarized in PDX 6-7 and set forth immediately below:



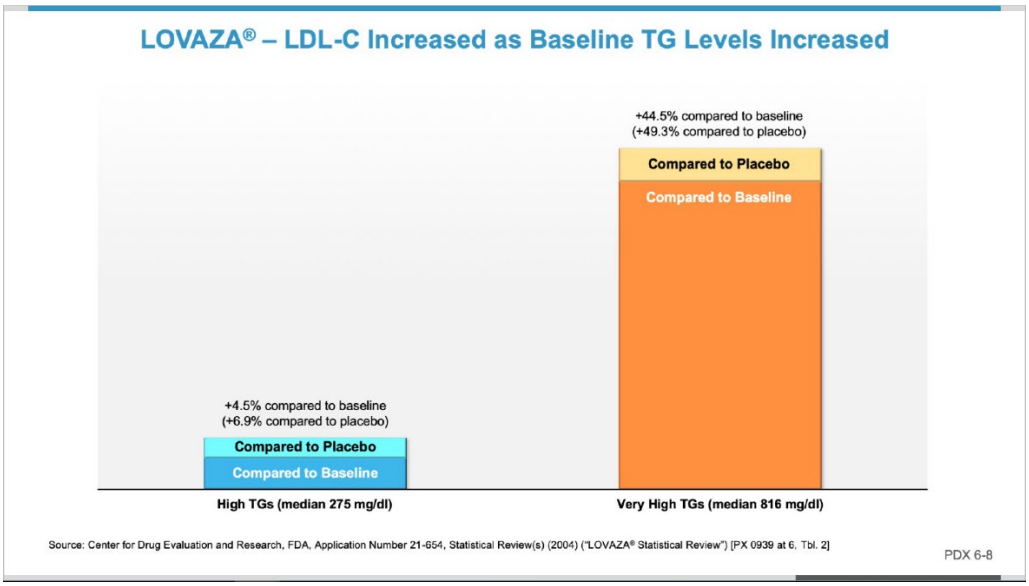
51. Observing these differential effects, Goodman & Gilman's *Pharmacologic Basis of Therapeutics*, a standard reference, wrote:

> In patients with mild hypertriglyceridemia (e.g., triglycerides <400 mg/dl), fibrate treatment decreases triglyceride levels by up to 50% and increases HDL-C concentrations about 15%; LDL-C levels may be unchanged or increase. *The second-generation agents, such as*

> *fenofibrate, bezafibrate, and ciprofibrate, lower VLDL levels to a degree similar to that produced by gemfibrozil, but they also are more likely to decrease LDL levels by 15% to 20%. In patients with more marked hypertriglyceridemia (e.g., 400 to 1000 mg/dl), a similar fall in triglycerides occurs, but LDL increases of 10% to 30% are seen frequently*.

PX 1027 (Goodman & Gilman 2006) at 31 (emphasis added); Trial Tr. 1584:20–1586:24 (Toth Direct).

52. Clinical studies with Lovaza similarly reported differential effects in patients with severe hypertriglyceridemia compared to patients with lower TG levels: LDL-C increases of approximately 45–50% in patients with TGs of at least 500 mg/dL, compared to LDL-C increases of only approximately ***4.5–7%*** in patients with less elevated TG levels. PX 939 (Lovaza Statistical Review) at 5–6; Trial Tr. 1587:4–1590:11 (Toth Direct). These differential effects of LDL-C in patients with severe hypertriglyceridemia compared to high TGs with Lovaza are summarized in PDX 6-8 and immediately set forth below:



53. Thus, as of March 2008, a person of ordinary skill in the art would have understood, first, that TG-lowering therapy would raise LDL-C in severely hypertriglyceridemic patients through enhanced conversion of VLDL to LDL, and second, that this was true even of drugs that

lowered or did not significantly raise LDL-C in patients with lower levels of elevated TGs. Trial Tr. 1574:3–1598:17 (Toth Direct).

D. Statins Were Not Approved for Treating Severely Hypertriglyceridemic Patients, and Were Not Reliably Effective in Reducing TGs

54. On the last day of trial, during cross-examination of Plaintiffs' expert Dr. Toth, Defendants identified for the first time the 2007 approved Lipitor labeling as prior art in support of an assertion that statins were approved to treat severe hypertriglyceridemia. *See* DX 3007 (Liptor Label 2007); Trial Tr. 1809:1–13 (statement of Mr. Klein). As explained below, Defendants' attempted reliance on statins in the prior art is procedurally improper and should not be permitted. *See infra* ¶¶ 735–38. In any event, statins were not approvedfor treatment of severe hypertriglyceridemia and are not reliably effective in reducing TGs in severely hypertriglyceridemic patients.

55. As Dr. Toth explained during cross-examination, Lipitor was approved for treatment of hypertriglyceridemia, not severe hypertriglyceridemia. Trial Tr. 1808:19–20 (Toth Cross) ("It had no indication to treat severe hypertriglyceridemia at all."); *id.* at 1971:8–10 (Toth Re-Direct) ("Q. And are statins approved to treat very high triglycerides? A. No."). Dr. Heinecke agreed that statins were not (and are not) approved to treat severe hypertriglyceridemia. Trial Tr. 842:13–16 (Heinecke Cross) ("Q: It is correct, is it not, Dr. Heinecke, that statins are not approved to treat very high triglycerides? A: It's correct that it's not approved . . . .").

56. The 2007 Lipitor Label made clear that the drug was indicated for treatment "Hypertriglyceridemia (Fredrickson Type IV)" and had not been studied in Fredrickson Type V, as would be required to obtain approval for treatment of severe hypertriglyceridemia. *See* DX 3007 (Liptor Label 2007) at 11, 15; Trial Tr. 1976:6–14 (Toth Re-Direct); *see also* PX 989 (ATP-III) at 190; DX 1876 (ATP-III) at 177 ("High triglycerides equate to the older definition of type 4 hyperproteinemia, whereas very high triglycerides were called type 5 hyperproteinemia."). Moreover, because the study referenced in the Lipitor label included patients both below and above 500 mg/dL and did not separately report the effects on either group, the labeling would not permit

one to draw any conclusions about the effects of the drug on patients above 500 mg/dL. Trial Tr. 1817:11–1818:7 (Toth Cross) (discussing DX 3007 (Liptor Label 2007) at 12, Tbl. 4).

57. The 2007 Lipitor label reported that some patients experienced a 40 or 50% increase in triglycerides from the drug, "not an effect you would want to see[]" in severely hypertriglyceridemic patients. DX 3007 (Lipitor Label 2007) at 12; Trial Tr. 1977:11–15 (Toth Re-Direct). The 2007 Lipitor label thus revealed that Lipitor was not a reliable treatment for severe hypertriglyceridemia. Other prior art was to similar effect. ATP-III, for example, stated that statins were not appropriate for use as a "first line agent for very high triglycerides" because "statins [are] not powerful triglyceride lowering drugs." *See* PX 989 (ATP-III) at 194; DX 1876 (ATP-III) at 181; Trial Tr. 1970:16–1971:3 (Toth Re-Direct). Similarly, the Bays 2008 review explained that statins only "modestly reduce triglyceride levels" and are "mainly . . . used to lower LDL-C levels. Other lipid-altering agents that are used more specifically to reduce TG levels include niacin, fibrates, and omega-3 fatty acids." *See* PX 486 (Bays 2008) at 2.

58. At the time of the invention, statins were understood to have a different mechanism of action for approved treatments for severe hypertriglyceridemia. As the Bays 2008 article noted, "Statins & P-OM3 [prescription omega-3 fatty acids] reduce TG levels by different mechanisms." PX 486 (Bays 2008) at 9. Statins were understood to inhibit the HMG-CoA enzyme, reducing cholesterol synthesis and increasing clearance of LDL through up-regulation of the LDL receptor. As Bays 2008 reported, the effect on TG levels was indirect: "[u]p-regulated LDL receptors may also increase clearance of other TG-containing lipoproteins, at least partially accounting for the modest TG lowering effects of statins." *See* PX 486 (Bays 2008) at 9; Trial Tr. 1975:3–15 (Toth Re-Direct). By contrast, there was no evidence that omega-3 fatty acids inhibit the HMG-CoA enzyme, and neither DHA or EPA was believed to act like a statin. Trial Tr. 1975:16–21. Instead, omega-3 fatty acids were repeatedly described in the prior art as reducing TGs in severely hypertriglyceridemic patients in the same way as fibrates and niacin: through enhanced conversion of the TG-rich VLDL particles to LDL particles. *See, e.g.,* PX 486 (Bays 2008) at 9–12; PX 923 (McKenney I) at 5; *see also* PX 289 (VASCEPA FDA Medical Review) at 14.

III. DEVELOPMENT OF THE CLAIMED METHODS OF TREATMENT

A. Conception of the Claimed Methods

59. Although an EPA-only drug product, Epadel, was first developed around 1990 by the Japanese drug company Mochida, Epadel purified EPA was not used to treat severe hypertriglyceridemia until approximately twenty years later when Amarin developed VASCEPA. DX 1528 (Epadel PI 2007) at 1. Before Amarin's contribution, EPA was used to treat hyperlipidemia, a condition involving mild to moderate elevations of cholesterol and/or triglycerides.[4] DX 1528 (Epadel PI 2007) at 2; *see also* Manku Dep. Tr. 40:24–41:15 (Nov. 7, 2018) (explaining that the hyperlipidemia indication for Epadel refers to patients with "mild to moderate levels of triglycerides . . . between 120 to 200 milligrams per deciliter"); Trial Tr. 1674:4–1675:18 (Toth Direct).

60. Prior to beginning to develop VASCEPA to treat severe hypertriglyceridemia, Amarin, and its predecessor Laxdale Limited, ("Laxdale"), had long studied EPA for use in neuropsychiatric indications. Manku Dep. 17:18–18:7, 18:9–19:6. In particular, Laxdale conducted a number of preclinical and clinical trials studying the use of purified EPA for depression, schizophrenia, and Huntington's Disease. Manku Dep. 24:22–26:18. While Laxdale was pursuing the Huntington's Disease indication, Amarin acquired Laxdale, including its clinical program. Manku Dep. 26:19–27:22, 30:18–31:4, 31:10–32:12. Each of Laxdale's clinical trials directed to the neuropsychiatric conditions ultimately failed. Manku Dep. 25:19–26:18, 33:17–34:1, 35:2–6.

61. However, the neuropsychiatric clinical program provided Amarin scientists with unprecedented access to well-controlled clinical study data concerning the effects of 1, 2, and 4 g of EPA per day in healthy volunteers and patients. *See, e.g.*, DX 1816 (Pre-IND Meeting Information Package) at 60–63; PX 289 (VASCEPA FDA Medical Review) at 25–27, VASCEPA

[4] In addition to hyperlipidemia, Epadel was also approved to treat the symptoms of arteriosclerotic ulceration and alleviation of pain and feeling of cold. DX 1528 (Epadel PI 2007) at 2; *see also* Trial Tr. 1674:4–21 (Toth Direct).

FDA Medical Review; *see also* Manku Dep. 153:22–154:4 (describing administration of 2- and 4-gram doses of EPA to schizophrenia patients); Manku Dep. 221:18–24 (referencing his "previous work" using a 2- and 4-gram doses of EPA).

62. At the time, Dr. Mehar Manku, the first-named inventor on the patents, served as Amarin's Vice President of Research and Development, and as a Laxdale scientist before that. Manku Dep. 31:19–22 ("My title [upon joining Amarin] was vice president of R&D or along those lines."). As Dr. Manku testified, he has "work[ed] in the area of fatty acids as medicines for the last almost 40 years or so and worked extensively using EPA . . . I was, and I have been, in this field for a very long time." Manku Dep. 10:8–13. Accordingly, Dr. Manku possessed vast experience and knowledge in the field of developing fatty acids as medicines.

63. After the failure of the neuropsychiatric program, Dr. Manku reviewed the clinical pharmacology data from those studies and began to focus on EPA's potential as a therapy for severe hypertriglyceridemia. Manku Dep. 79:21–80:25. Dr. Manku observed that a problem existed because use of the approved fish oil product on the market caused an increase in LDL-C. Manku Dep. 39:15–40:5. Strikingly, and in an insight found nowhere in the prior art, Dr. Manku observed from the neuropsychiatric clinical data that "DHA actually interferes with the mode of action of EPA." Manku Dep. 86:2–8. This insight, and the underlying clinical data, lead Dr. Manku to a new understanding of the effects of EPA on plasma lipids and other biomarkers, as well as the way DHA may interfere with those effects. *See id.* at 89:6–93:12.[5] Based on this understanding, he realized that purified EPA, in the absence of DHA, could reduce TGs in severely hypertriglyceridemic patients without raising LDL-C. This belief was then solidified by clinical

[5] Similarly, Dr. Manku looked to dose-ranging studies that Laxdale conducted as part of its schizophrenia clinical program and recognized the effects that a 4 g dose would have on fatty acid content and biomarker levels in the blood. Manku Dep. 153:13–16, 153:18–154:4 (noting that a 4-g dose of purified EPA reduced arachidonic acid); *id.* at 84:9–86:18 (explaining how his decades of experience analyzing EPA blood samples resulted in a deep understanding of EPA's effects on biochemical pathways and biomarkers); *see also* DX 1816 (Pre-IND Meeting Information Package) at 63 (noting that 4 g of EPA increased "DPA, a metabolite of EPA . . . without any changes in DHA" and also decreased arachidonic acid).

data Dr. Manku obtained in March 2008 from a trial studying the effects of EPA in schizophrenic patients sponsored by Amarin's predecessor, Laxdale. As Dr. Manku testified, drug treatment for schizophrenia patients drives large increases in TGs, but the blood data from the schizophrenia study reported that EPA reduced TGs in those patients without raising LDL-C. *See* DX 1857 (Mar. 25, 2008 M. Manku E-mail) at 1; M. Manku Dep. 162:5–164:16; *see also id.* at 95:8–11 ("[C]lozapine is a drug that is used for treatment of schizophrenia . . . [and] is notoriously known to elevate triglycerides").

64. Dr. Manku's insights were contrary to the conventional wisdom at the time and wholly outside the knowledge of one of ordinary skill. Dr. Heinecke testified that a POSA would not have viewed the Amarin-sponsored neuropsychiatric studies as relevant to the use of EPA in severely hypertriglyceridemic patients. Trial Tr. 913:12–914:3 (Heinecke Re-Direct). Dr. Manku acknowledged that "somebody else looking into this data could think differently, but I was thinking in very different way on it because of my expertise in this field . . . ." Manku Dep. 163:15–18.

65. During this time, and by early 2008, Dr. Manku was also educating his colleagues that EPA would work differently from prior medications when reducing TGs in severely hypertriglyceridemic patients. *See* Manku Dep. 140:7–141:24 ("I was trying to convince my colleagues: Look, this is . . . going to be a different type of mechanism."). For example, when discussing the schizophrenia data, Dr. Manku testified that he further used that data in an effort "to convince [his] colleagues that: Look, there is here bits and pieces of information, although not in the right population." Manku Dep. 163:19–22; PX 476 at 1 (Mar. 25, 2008 M. Manku E-mail) (discussing EPA's effects in schizophrenia patients); *see also* PX 475 (Mar. 16, 2008 M. Manku E-mail) at 1 (pointing his colleagues to preclinical data); PX 472 (Mar. 24, 2008 M. Manku E-mail) at 1 (describing his views on how EPA affects lipids and biomarkers such as LDL and Lp-PLA2).

66. Although convincing individuals inside and outside the company was no easy task, Dr. Manku's insights eventually won out. *See* Manku Dep. 82:9–18 (testifying that he had "great difficulty in convincing individuals within the company, and outside the company, on why ethyl-

EPA would be effective in lowering triglycerides significantly in very high patient population, with those over 500 [mg/dL], and would not affect other lipid parameters"); *see also* Manku Dep. 82:20–83:1, 83:3–5, 83:7–10 (explaining that "it took a long time to convince" his Amarin colleagues before they moved forward with the clinical program). At that point, Dr. Manku then worked with his co-inventors to pursue an indication for purified EPA for the treatment of severe hypertriglyceridemia, including by designing a clinical program to prove that purified EPA was effective to treat severe hypertriglyceridemia. *See, e.g.*, PX 755 (Mar. 10, 2008 I. Osterloh E-mail) at 3 (explaining the rationale for and contemplated components of Amarin's severe hypertriglyceridemia clinical program); Osterloh Dep. 119:3–121:8 (Nov. 7, 2018) (testifying regarding same); DX 1886 (Jan. 23, 2008 I. Osterloh E-mail) at 1 (conferring with co-inventor, Dr. Pierre Wicker, regarding design of clinical studies to support the development of EPA for severe hypertriglyceridemia); Osterloh Dep. 138:16–22, 139:20–22, 139:24–140:6, 140:8–10, 140:12–141:11 (testifying about DX 1886 and explaining that in early 2008, the inventors were preparing to consult with experts "on the design and conduct of the clinical trial program").

67. As is evident from these e-mails, Amarin and the inventors had conceived of the inventions described in the Asserted Claims by March 2008. *See, e.g.*, Manku Dep. 131:15–19; Manku Dep. 132:1–2, 132:4, 132:6–17.

B. Clinical Development of the Claimed Methods of Treatment

68. Thereafter, Amarin pursued a two-part clinical program to support FDA approval of a purified EPA pharmaceutical product. To that end, beginning in May 2008, Amarin proposed a clinical program to prove the effectiveness of EPA in treating severe hypertriglyceridemia (the "MARINE" study), along with a second clinical program to show EPA's favorable action on biomarkers of CV risk in mixed dyslipidemia (the "ANCHOR" study). *See* PX 482 at 4, ¶¶ 9–10, May 9, 2008 Ltr. From Amarin to FDA Requesting Pre-IND Meeting (Pre-IND FDA Meeting Request); Trial Tr. 72:14–74:11 (Ketchum Direct).

69. During this time, in order to obtain investor support for the clinical program, Dr. Manku and his colleagues assembled published literature to bolster Dr. Manku's insight

concerning the clinical benefits of EPA. *See, e.g.*, DX 1884 (Mar. 19, 2008 I. Osterloh E-mail) at 1–2 (addressing the "line we should take with investors"); Osterloh Dep. 102:9–23 (testifying about DX 1884 and explaining that Amarin would discuss published literature with investors without "go[ing] into the details or differences between various studies and the patient population in them"); DX 1800 (Mar. 2010 Amarin Investor Presentation) (listing relevant published literature for investors).

70. Amarin provided the same literature support, along with Amarin's proprietary clinical data from the neuropsychiatric programs, in its submissions to FDA. DX 1816 (Pre-IND Meeting Information Package) at 60–67 (discussing Amarin-sponsored studies), 67–77 (discussing published literature).

71. FDA ultimately approved Amarin's clinical program, allowing Amarin to move forward with the MARINE Trial—the clinical trial studying the effects of purified EPA (AMR101) in patients with severe hypertriglyceridemia. Trial Tr. 78:10–79:16 (Ketchum Direct); PX 482 (Pre-IND FDA Meeting Request) at 13 (providing in the minutes from the FDA meeting that the MARINE clinical trial "could potentially suffice for th[e severe hypertriglyceridemia] indication . . . provided that the results are robust."); *see also* Trial Tr. 72:14–18 (Ketchum Direct) (confirming that AMR101 was the code identifier for VASCEPA that was used during development). However, because EPA was a new chemical entity—that is, an active ingredient that had not been previously approved by FDA—and because Amarin was proposing to use EPA for a chronic indication—reduction in TGs in severely hypertriglyceridemic patients—FDA required Amarin to conduct long-term carcinogenicity trials. PX 482 (P-IND FDA Meeting Request) at 11; *see also* Trial Tr. 111:5–10 (Ketchum Direct) (explaining that a "new chemical entity" is "basically, a chemical compound that has never been approved before"). Specifically, in the minutes from the July 2008 Pre-IND Meeting, FDA explained that "it is generally expected that a carcinogenicity study be conducted in two rodent species to support the marketing approval of *a new chemical entity* for *a chronic use indication*." PX 482 (Pre-IND FDA Meeting Request) at 11 (emphasis added); Trial Tr. 108:20–111:10 (Ketchum Direct) (explaining that Amarin was

required to perform carcinogenicity studies because such studies are "an important component particularly for new chemical entities and chronically administered drugs").

72. In addition, before undertaking the MARINE trial, Amarin assembled a group of experts in December 2008 to advise it on the trial design and the likely effects EPA would have on the lipid profiles of severely hypertriglyceridemic patients. At the expert panel meeting, the experts expressed skepticism that EPA could be used to reduce TGs in these patients without raising their LDL-C. PX 754 (Expert Panel Notes) at 2.[6] In fact, the experts expressly opined that "LDL-C is likely to go up as it does with virtually all TG-lowering therapies in this group of patients." PX 754 (Expert Panel Notes) at 2; Osterloh Dep. 186:4–24, 187:4 (testifying about his notes and explaining that he did not recall any expert at the meeting expressing a contrary view; "I believe that no-one in the panel, none of the experts, invited experts, expressed a contrary view otherwise I would have recorded it as a mixed opinion from the experts on the topic."). *See generally* Osterloh Dep. Tr. 180:9–182:9, 182:11–184:14, 184:16–185:20, 185:22–186:24, 187:1–4 (testifying regarding the December 2008 Expert Panel and his notes from same).

73. Despite the outside experts' skepticism, Amarin nevertheless moved forward with the MARINE trial. The trial first read out in late 2010. *See* PX 807 (MARINE CSR) at 3, (the study database was unblinded on November 16, 2010); Trial Tr. 79:3–6 (Ketchum Direct) (explaining that the MARINE trial began in 2009 and concluded towards the very end of 2010). As reported in the MARINE Clinical Study Report, the MARINE trial demonstrated a 33% reduction in TGs, a 2% reduction in LDL-C, and a 9% reduction in apo B, compared to placebo. *See, e.g.*, PX 807 (MARINE CSR) at 8–9; Trial Tr. 97:20–98:7 (Ketchum Direct); *see also* Trial Tr. 95:2–8 (Ketchum Direct) ("[T]he MARINE study robustly met its primary efficacy endpoint and also achieved its secondary efficacy endpoints and on down in through the exploratory endpoints, and it established a safe and tolerable profile as well."); Trial Tr. 1604:6–1606:8 (Toth

[6] These notes are also available in the record at pages 3–6 of DX 1860.

Direct); PX 807 (MARINE CSR) at 70–90 (detailing effects of EPA on the MARINE subjects' lipid and other biomarker levels).

74. Consistent with Dr. Manku's insights regarding the effects of EPA in severely hypertriglyceridemic patients, the MARINE Clinical Study Report explicitly states that"[i]n contrast to other TG-lowering agents, the reduction in TG levels was not associated with an elevation in LDL-C levels compared to placebo." PX 807 (MARINE CSR) at 11; Trial Tr. 1604:19–1605:21 (Toth Direct).

75. Following the results of the MARINE trial, clinicians repeatedly praised VASCEPA's ability to lower TGs in severely hypertriglyceridemic patients while avoiding increases in LDL-C. *See* Trial Tr. 1606:20–1615:17, 1722:2–1723:13 (Toth Direct).

76. For example, Dr. Richard Castaldo of the Niagara Falls Memorial Medical Center reported that "[s]witching statin add-on therapy from fibrate to icosapent ethyl [VASCEPA] maintained or improved the lipid profile and was well tolerated with no adverse reactions in a series of patients with hypertension and high cardiovascular risk" and that "important differences between icosapent ethyl and other add-on therapy options include its good safety and tolerability profile and the fact that it does not increase LDL-C levels, as supported by clinical studies and the icosapent ethyl product label." PX 866 (Castaldo) at 6.

77. Similarly, Dr. Jonathan Fialkow of the Miami Cardiac and Vascular Institute observed that "[u]se of products containing both DHA and EPA . . . require periodic monitoring of LDL-C during therapy due to the potential for increases in this lipid parameter, while treatment with the EPA-only product, icosapent ethyl [VASCEPA] has no LDL-C monitoring requirement." PX 852 (Fialkow) at 5.

78. In reference to the MARINE trial results, Dr. Darren McGuire of University Texas Southwestern observed that "[a]t the end of the day, if you can have favorable cardiovascular effects without raising LDL cholesterol, that's going to be an advantage." DX 1581 (O'Riordan) at 1.

79. The observations of Dr. Steven Nissen, the former chief of cardiology at the Cleveland Clinic, after learning of the topline results of the MARINE trial were to similar effect indicated that VASCEPA's ability to lower TGs in individuals with very high TG levels without increasing LDL-C has been recognized as a "real advance in the treatment of elevated triglycerides" because "It gives you all the benefit without the downside." DX 1581 (O'Riordan) at 2; Trial Tr. 1610:13–1612:24, 1723:2–13 (Toth Direct). Dr. Nissen regarded the topline results as exciting, commenting that the MARINE trial showed that "[t]here's still room for small companies to do innovative things in this field."[7] DX 1581 (O'Riordan) at 2.

IV. VASCEPA

A. VASCEPA's FDA Approval

80. Anyone wishing to market a new drug that has not previously been approved by the FDA (a "pioneering" drug) must file a New Drug Application ("NDA") demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b).

81. Based on the results of the MARINE study, in 2011 Amarin filed an NDA (No. 202057) seeking FDA approval to market 1 g icosapent ethyl capsules, under the tradename VASCEPA, for use in treatment of patients with severe hypertriglyceridemia. Trial Tr. 101:14–102:19 (Ketchum Direct).

82. When it approved VASCEPA, the FDA publicly released a Medical Review, a report that detailed the FDA medical reviewer's evaluation of Amarin's clinical safety and efficacy data and the reviewer's rationale for recommending FDA approval of the 4 g per day dosage of VASCEPA. Trial Tr. 102:20–103:7 (Ketchum Direct); PX 289 (VASCEPA FDA Medical Review).

[7] While Dr. Nissen noted some potential caveats about the size, duration, and lack of peer review of the MARINE trial, FDA ultimately had such no concerns about the study design of the MARINE trial (including size and duration) when approving VASCEPA for the treatment of severe hypertriglyceridemia. Trial Tr. 1611:10–1612:6 (Toth Direct). Moreover, the results of the MARINE trial, which had only just been announced when Dr. Nissen offered his caveats, were ultimately published in a peer reviewed publication, the *American Journal of Cardiology*. Trial Tr. 1612:7–13 (Toth Direct).

83. The FDA's Medical Review is publicly available online and "reflects important background information that a [physician] would understand and bring to bear when using [VASCEPA or] [D]efendants' ANDA products as indicated." Trial Tr. 671:2–6 (Sheinberg Cross); *see also* Trial Tr. 102:20–103:2 (Ketchum Direct); Mathers Dep. 89:1–5, 89:24–90:4. The Medical Review sheds further light on FDA's rationale for approving VASCEPA and the scope of that approval. Mathers Dep. 90:24–91:4.

84. The Medical Review reflects that FDA approved VASCEPA for a chronic indication. The review includes a checklist intended to guide the medical reviewer's assessment of whether a given NDA is complete and meets FDA's safety, efficacy, and other requirements for approval. Trial Tr. 105:11–18, 105:25–106:6 (Ketchum Direct). One section of the checklist asks whether, for safety purposes, the drug has been used in a sufficient number of patients. In the case of VASCEPA, the reviewer specifically noted that VASCEPA met the patient-exposure guidelines for "chronically administered drugs," while also marking that requirements "[f]or drugs not chronically administered (intermittent or short course)" were not applicable to VASCEPA. PX 289 (VASCEPA FDA Medical Review) at 142; *see also* Trial Tr. 106:14–108:14 (Ketchum Direct).

85. The Medical Review includes a section identifying "Important Safety Issues" that FDA has observed with "Related Drugs." PX 289 (VASCEPA FDA Medical Review) at 14. The very first safety concern noted by the medical reviewer was Lovaza's effect on LDL-C. *Id.* The reviewer noted that "the only other FDA approved omega-3 fatty acid product (Lovaza)" has "four areas of potential safety concern," beginning with "increases in LDL-C." *Id.*; *see also* Sheinberg Tr. 671:15–672:1 (Sheinberg Cross). The reviewer explained that "[t]he increase in LDL-C" observed with Lovaza "is thought to be due to the . . . enhance[d] conversion of [VLDL] and [IDL] to LDL-C." PX 289 (VASCEPA FDA Medical Review) at 14. When later discussing the MARINE data, the medical reviewer specifically noted that "Vascepa 4 g did not increase LDL-C levels." *Id.* at 58.

86. The Medical Review also demonstrates that FDA approved VASCEPA 4 g per day based on its ability to reduce TGs in adult patients with severe hypertriglyceridemia and maintain

that reduction through at least 12 weeks. In Section 6.1.9, which is entitled "Discussion of Persistence of Efficacy and/or Tolerance Effects," the medical reviewer contrasted the effects of VASCEPA 4 g per day with those observed in the 2 g and placebo groups, explaining that only the 4 g dose reduced TGs and maintained that reduction throughout the 12 week study. PX 289 (VASCEPA Medical Review) at 68–69; *see also* Trial Tr. 103:12–104:16 (Ketchum Direct); Mathers Dep. 92:10–16, 93:3–8, 93:10–11. The medical reviewer "interpreted this as a more potent effect of the Vascepa 4 g dose; i.e. the ability to eliminate the wide TG fluctuations" when used for extended periods. PX 289 (VASCEPA FDA Medical Review) at 55. FDA approved VASCEPA 4 g per day because of this demonstrated persistence of effect—meaning its ability to reduce TGs in patients with severe hypertriglyceridemia and maintain that reduction. Mathers Dep. 94:22–25, 95:2–5, 96:2–5, 96:7–17; *see also* Trial Tr. 1338:16–1339:6, 1334:3–21 (Peck Direct).

87. On July 26, 2012, FDA approved VASCEPA (icosapent ethyl) 1 g capsules "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." Trial Tr. 51:20–52:3 (Ketchum Direct); Trial Tr. 65:11–20 (Ketchum Direct); PX 266 (NDA Approval Letter (July 26, 2012)) at 1–6, 17; *see also* PX 1186 (VASCEPA Label 2019) at 1–2.

88. FDA approved a 500 mg strength of VASCEPA in February 2017. Joint Stipulations of Fact ¶ 181 (ECF No. 324). Thus, Amarin currently markets VASCEPA in both 1 g and 500 mg capsules. *See* PX 1186 (VASCEPA Label 2019) at 2; Joint Stipulations of Fact ¶¶ 181–82, 201 (ECF No. 324). And, the daily dose of VASCEPA is 4 g per day, taken as two 1-g (or four 500 mg) capsules twice daily with food. *See* PX 1186 (VASCEPA Label 2019) at 2; Joint Stipulation of Fact ¶ 202 (ECF No. 324).

89. Amarin Pharmaceuticals Ireland Limited is the current holder of NDA No. 202057. Joint Stipulations of Fact ¶ 178 (ECF No. 324).

90. Amarin Pharma, Inc. is Amarin Pharmaceuticals Ireland Limited's agent in the United States for purposes of communicating with FDA regarding NDA No. 202057. Joint Stipulations of Fact ¶ 179 (ECF No. 324).

B. VASCEPA's Approved Prescribing Information

91. Upon approving VASCEPA in 2012, FDA also approved prescribing information for VASCEPA that informs clinicians how to use the drug with their severely hypertriglyceridemic patients. Trial Tr. 344:3–20 (Budoff Direct).

92. The approved prescribing information—also called the label, labeling, or package insert—includes a statement of the approved indication, instructions on when and how to administer the drug, and the underlying clinical data supporting the indication. Trial Tr. 344:3–20 (Budoff Direct); *see also* Trial Tr. 343:11–14 (Budoff Direct) (explaining that the package insert also goes by the names "label or package insert or prescribing information"); Trial Tr. 1324:13–18 (Peck Direct).

V. THE MARINE PATENTS

A. Prosecution of the MARINE Patents

93. Mehar Manku, Ian Osterloh, Pierre Wicker, Rene Braeckman, and Paresh Soni are named as inventors of the Asserted Patents. Joint Stipulations of Fact ¶ 12 (ECF No. 324).

94. The U.S. Applications that ultimately issued as the Asserted Patents are continuations of U.S. Application No. 12/702,889, filed on February 9, 2010, which ultimately issued as U.S. Patent No. 8,293,727 ("the '727 Patent"). Joint Stipulations of Fact ¶ 10 (ECF No. 324).

95. The Asserted Patents further claim priority to U.S. Provisional Application No. 61/151,291 (DX 1522), filed on February 10, 2009, and U.S. Provisional Application No. 61/173,755 (DX 1523), filed on April 29, 2009. Joint Stipulations of Fact ¶ 11 (ECF No. 324). The Provisional Applications detail the effects of purified EPA on multiple plasma lipids and biomarkers, including TGs, LDL-C, and apo B. *See* DX 1522 (Feb. 2009 Provisional Application) at 5–6; DX 1523 (April 2009 Provisional Application) at 12–13. Additionally, the Provisional Applications describe in detail the MARINE Clinical Study design—including, among other things, the patient population to be studied and various plasma lipid levels and biomarkers designated as secondary efficacy variables. *See* DX 1522 (Feb. 2009 Provisional Application) at

18–24; DX 1523 (April 2009 Provisional Application) at 25–31. These effects were later confirmed by the MARINE trial results. *See infra* ¶¶ 73–74, 111.

96. During the prosecution of the Asserted Patents, Amarin submitted several declarations, from multiple experts including Dr. Harold Bays and Dr. Howard Weintraub, to the United States Patent and Trademark Office ("USPTO") in support of patentability. *See, e.g.*, PX 38 ('727 Patent File History) at 129–31 (Bays I Declaration), 170–72 (Weintraub I Declaration), 976–84 (Weintraub II Declaration),1211–26 (Bays II Declaration), 1710–18 (Bays III Declaration). For example, in the Bays I Declaration, Dr. Bays submitted and discussed the results of the MARINE Clinical Study, and expressed his surprise that AMR101 reduced triglycerides in severely hypertriglyceridemic patients without causing a statistically significant increase in LDL-C. PX 38 ('727 Patent File History) at 130, ¶¶ 12–13 (Bays I Declaration); PX 38 ('727 Patent File History) at 140–48 (attaching the results of the MARINE Clinical Study).

97. Amarin also submitted two declarations by Dr. Philip Lavin, a biostatistician. *See, e.g.*, PX 38 ('727 Patent File History) at 1233–37 (Lavin I Declaration), 1725–29 (Lavin II Declaration). In those declarations, Dr. Lavin evaluated conclusions drawn by the Patent Examiner about three pieces of prior art. *See, e.g.*, PX 38 ('727 Patent File History) at 1233–37 (Lavin I Declaration); PX 38 at 1725–29 (Lavin II Declaration). Specifically, these declarations addressed the statistical likelihood that subjects with certain baseline triglyceride levels were included in the studies disclosed in the prior art references. *See, e.g.*, PX 38 ('727 Patent File History) at 1233–37 (Lavin I Declaration), 1725–29 (Lavin II Declaration).

98. When allowing the claims of the '727 Patent, the Patent Examiner included a detailed Statement of Reasons for Allowance in accordance with 37 C.F.R. § 1.104(e) and the specific guidance set forth in section 1302.14 of the Manual of Patent Examination Procedure. PX 38 ('727 Patent File History) at 1829–35. In the Notice of Allowance, the Examiner expressly noted that the claimed methods of treatment are not anticipated and then relied upon the evidence demonstrating objective indicia of non-obviousness for the invention in allowing the claims. *Id.* Defendants have not asserted anticipation here, and Defendants' expert

conceded he had no basis to contradict the Examiner's finding that the claims were not anticipated. Trial Tr. 906:9–11 (Heinecke Cross).

99. In granting the '727 Patent, the Examiner relied on objective indicia of non-obviousness—in particular, a showing that the applicants demonstrated unexpected results (an unexpected reduction in apo B), and satisfied a long-felt unmet medical need through their invention of a method of treatment that lowered triglycerides in persons with very high triglycerides without substantially increasing LDL-C, as prior art treatments had done. PX 38 ('727 Patent File History) at 1831–34.

100. 37 C.F.R. § 1.104(e) provides that "[i]f the examiner believes that the record of the prosecution as a whole does not make clear his or her reasons for allowing a claim or claims, the examiner may set forth such reasoning." Accordingly, as authorized by 37 C.F.R. § 1.104(e), the Examiner made the prosecution history record clear by discussing the specific reasons why the claims were patentable in the Reasons for Allowance. PX 38 ('727 File History) at 1829–35 (Notice of Allowance).

101. Specifically, in the Examiner's Statement of Reasons for Allowance of the claims of the '727 Patent, the Examiner characterized the claims as "a very narrow and specific method," and summarized the claims as follows:

> Patient population: TG levels between 500 mg/dL and 1500 mg/dL (very high) not receiving any lipid altering therapy,
>
> Drug: 96% pure ethyl-EPA with substantially no DHA
>
> Amount: 4 g per day
>
> Dose regimen: at least 12 weeks.

PX 38 ('727 Patent File History) at 1829–30.

102. After describing the scope of the claims, the Examiner next found that the claims were not anticipated. As noted above, Defendants do not challenge this finding.

103. The Examiner concluded that it would have been *prima facie* obvious to treat patients having TG above 500 mg/dL with 96% pure ethyl-EPA. *See, e.g.*, PX 38 ('727 Patent File History) at 1830.

104. Nevertheless, the Examiner found the pending claims patentable because "Applicant was able to overcome the above 103 obviousness rejection by showing: 1 - Unexpected results, and 2 - Long felt unmet medical need." *See, e.g.*, PX 38 ('727 Patent File History) at 1831 (Notice of Allowance). The Examiner then spent more than three pages specifically reviewing the evidence of objective indicia supporting the Examiner's ultimate conclusion that the claims were patentable. *See, e.g.*, *id* at 1831–34.

105. In these pages, the Examiner discussed at length the September 11, 2011 Weintraub and May 16, 2012 Bays declarations and how they evidenced the objective indicia of unexpected results and long-felt unmet medical need that overcame the Examiner's prima facie obviousness rejection. *See, e.g.*, *id.* These were the only declarations discussed in the Examiner's Reasons for Allowance. *See, e.g.*, *id.*

106. The Examiner's Statement of Reasons for Allowance tracks the guidance provided by MPEP § 1302.14(II)(A), which instructs the examiner to state which arguments and affidavits led to allowance when "claims are allowed on the basis of one (or some) of a number of arguments and/or affidavits presented, and a statement is necessary to identify which of these arguments and evidence were found to be most persuasive." *See* Trial Tr. 908:4–16 (Heinecke Cross). The Statement for Reasons of Allowance clearly identifies which affidavits the Examiner relied upon because the Examiner expressly stated that the September 11, 2011 Weintraub and May 16, 2012 Bays declarations provided the basis for overcoming the *prima facie* showing of obviousness by establishing both unexpected results and long-felt, but unmet, need in the prior art. PX 38 ('727 Patent File History) at 1831–34 (Notice of Allowance). In contrast, the Examiner did not cite to the Lavin Declarations, which are unrelated to objective indicia, the basis on which the Examiner granted the patents. *Id.* at 1233–37 (Lavin I Declaration), 1725–29 (Lavin II Declaration); *see also* Trial Tr. 908:17–20 (Heinecke Cross).

107. The Examiner included a Statement of Reasons for Allowance when allowing the claims of each of the Asserted Patents. Each Statement of Reasons for Allowance contains materially identical reasons for allowing the claims. *See* PX 39 ('728 Patent File History) at 6691–98; PX 40 ('715 Patent File History) at 6484–94; PX 41 ('677 Patent File History) at 6420–27; PX 42 ('652 Patent File History) at 6359–67; PX 50 ('560 Patent File History) at 8141–48; PX 51 ('929 Patent File History) at 547–54.

108. Pursuant to 21 U.S.C. § 355(b)(1), the Asserted Patents are among the patents listed in the Orange Book—a Food and Drug Administration ("FDA") publication formally known as *Approved Drug Products with Therapeutic Equivalence Evaluations*—in connection with NDA No. 202057. Joint Stipulations of Fact ¶ 13 (ECF No. 324).

B. Disclosure of the MARINE Patents

109. Each of the Asserted Patents is entitled "METHODS OF TREATING HYPERTRIGLYCERIDEMIA." Joint Stipulations of Fact ¶ 9 (ECF No. 324).

110. The shared specification of the Asserted Patents discusses a number of biomarkers that EPA may affect. In particular, the specification conveys Dr. Manku's insights on how EPA's mechanism of action in the body would affect nearly two dozen plasma lipids and biomarkers, including apo B and LDL-C. *See, e.g.*, PX 21 ('728 Patent) at 14.

111. In addition, the specification describes in detail the MARINE Clinical Study design, including the various plasma lipid levels and biomarkers designated as secondary efficacy variables. *See, e.g.*, PX 21 ('728 Patent) at 19–20. These effects were ultimately confirmed by the MARINE trial results, which were submitted to the Patent Office prior to allowance of the claims. PX 38 ('727 File History) at 130 (Bays I Declaration ¶¶ 12–13); PX 38 ('727 Patent File History) at 140–48 (attaching the results of the MARINE Clinical Study).

C. Ownership of the MARINE Patents

112. Amarin Pharmaceuticals Ireland Limited is the owner of the Asserted Patents. Joint Stipulations of Fact ¶ 8 (ECF No. 324).

D. Asserted Claims

113. The Asserted Claims consist of a total of ten claims from six patents—Claims 1 and 16 from the '728 Patent, Claim 14 from the '715 Patent, Claims 1 and 8 the '677 Patent", Claim 1 of the '652 Patent, Claims 4 and 17 of the '560 Patent, and Claims 1 and 4 of the '929 Patent. *See supra* ¶ 9.

114. Claim 1 of the '728 Patent is an independent claim. It recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

PX 21 ('728 Patent) at 21.

115. Claim 16 of the '728 Patent depends from Claim 1 of the '728 Patent. As a dependent claim, Claim 16 incorporates the limitations in Claim 1. Claim 16 of the '728 Patent recites:

> The method of claim 1, wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined.

PX 21 ('728 Patent) at 22.

116. Claim 14 of the '715 Patent is a dependent claim that depends on Claim 13 of the '715 Patent. As a dependent claim, Claim 14 incorporates the limitations in Claim 13.

117. Claim 13 of the '715 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, comprising administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by

> weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters for a period of at least 12 weeks to effect a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or apolipoprotein B in the subject.

PX 22 (’715 Patent) at 22.

118. Claim 14 of the ’715 Patent recites:

> The method of claim 13 comprising administering to the subject about 4 g per day of the pharmaceutical composition to effect a statistically significant reduction in triglycerides and apolipoprotein B without effecting a statistically significant increase of [LDL-C] in the subject.

PX 22 (’715 Patent & Certificate of Correction) at 22–23.

119. Claim 1 of the ’677 Patent is an independent claim. Claim 1 of the ’677 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of at least about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control.

PX 25 (’677 Patent) at 21.

120. Claim 8 of the ’677 Patent depends from Claim 1 of the ’677 Patent. As a dependent claim, Claim 8 incorporates the limitations in Claim 1. Claim 8 of the ’677 Patent recites:

> The method of claim 1, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of at least about 12 weeks to effect a reduction in apolipoprotein B compared to placebo control.

PX 25 (’677 Patent) at 22.

121. Claim 1 of the ’652 Patent is an independent claim. It recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by

> weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline.

PX 26 ('652 Patent) at 22.

122. Claim 4 of the '560 Patent depends from Claim 1 of the '560 Patent. As a dependent claim, Claim 4 incorporates the limitations in Claim 1.

123. Claim 1 of the '560 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject.

PX 30 ('560 Patent) at 22.

124. Claim 4 of the '560 Patent recites:

> The method of claim 1, wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject.

PX 30 ('560 Patent) at 23.

125. Claim 17 of the '560 Patent depends on Claim 11 of the '560 Patent. As a dependent claim, Claim 17 incorporates the limitations in Claim 11.

126. Claim 11 of the '560 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject compared to placebo control.

PX 30 ('560 Patent) at 23.

127. Claim 17 of the '560 Patent recites:

> The method of claim 11, wherein said administering effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control.

PX 30 ('560 Patent) at 23.

128. Claim 1 of the '929 Patent is an independent claim. Claim 1 of the '929 Patent recites:

> A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl comprising, orally administering to the subject daily for at least about 12 weeks a pharmaceutical composition comprising about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids.

PX 31 ('929 Patent) at 22–23.

129. Claim 5 of the '929 Patent depends from Claim 1 of the '929 Patent. As a dependent claim, Claim 5 incorporates the limitations in Claim 1. Claim 5 of the '929 Patent recites:

> The method of claim 1, wherein 12 weeks of said daily administration is effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dL.

PX 31 ('929 Patent) at 23.

VI. FURTHER CLINICAL DEVELOPMENT OF VASCEPA

A. The Need to Address Residual Cardiovascular Risk

130. As of 2008, atherosclerotic cardiovascular disease was "the leading cause of morbidity and mortality in industrialized societies." DX 1604 (Oram) at 1; Trial Tr. 898:13–899:14 (Heinecke Cross). That still remains true today. Trial Tr. 899:15–16 (Heinecke Cross).

131. It also has long been understood that, even with intensive cholesterol lowering, statins reduce cardiovascular events by only one-third, and therefore a large residual risk remains—leaving two-thirds of cardiovascular risk (strokes, heart attacks, etc.) unaddressed. DX 1604 (Oram) at 1; Trial Tr. 899:17–900:8 (Heinecke Cross); Trial Tr. 149:11–18 (Ketchum Direct). As of 2008, "this large residual disease burden ha[d] directed the attention of biomedical investigators and the pharmaceutical industry to other potential targets for drug development." DX

1604 (Oram) at 1; Trial Tr. 899:17–900:8 (Heinecke Cross). Therefore, as of March 2008, researchers were focused on trying to reduce residual cardiovascular risk, with scientists pursuing a variety of medical approaches, including various interventions to raise HDL. Trial Tr. 900:3–901:21 (Heinecke Cross) (acknowledging "intense interest" in raising HDL at the time); Trial Tr. 1730:12–24 (Toth Direct). These efforts were part of a more general longstanding interest, pursued for decades leading up to 2008, of reducing cardiovascular risk. Trial Tr. 1730:3–20 (Toth Direct). But as of March 2008, no TG-lowering drug had been demonstrated to reduce cardiovascular risk on top of a statin. Trial Tr. 1730:21–24 (Toth Direct).

132. Additionally, at the time of the invention, no approved treatment for severe hypertriglyceridemia had been shown to both lower TGs *and* reduce CV risk in patients with very high TGs. Trial Tr. 1625:14–21 (Toth Direct); Trial Tr. 842:19–843:17 (Heinecke Cross); DX 1876 (ATP-III) at 181, Tbl. VII.2-4; PX (ATP-III) at 194. To the contrary, because all approved treatments for severe hypertriglyceridemia at the time dramatically raised LDL-C, the prevailing concern was that treatment for severe hypertriglyceridemia exacerbated cardiovascular risk. Trial Tr. 1574:8–21 (Toth Direct) (all approved TG-lowering agents produced large increases in LDL-C); Trial Tr. 1577:13–25 (Toth Direct) ("[I]f the LDL shoots up, this would heighten risk for the development of cardiovascular disease."). For this reason, statins were often administered to severely hypertriglyceridemic patients along with their TG-lowering therapy, (*see* Trial Tr. 809:18–810:10 (Heinecke); Trial Tr. 1598:18–1599:18 (Toth Direct)), or stepwise added to that therapy once TGs were brought below 500 mg/dL, to address the enhanced cardiovascular risk. PX 288 (Karalis) at 10 (explaining that reducing triglycerides are the first goal when treating severely hypertriglyceridemic patients, but that "once the TG are lowered consideration should be given to adding a statin to their TG-lowering therapy"). There was accordingly a need for a TG-lowering agent that would significantly reduce cardiovascular risk on top of statin, including in patients with severe hypertriglyceridemia.

133. It was in this context that Amarin pursued additional clinical development of VASCEPA, including the REDUCE-IT Trial. Trial Tr. 140:3–8 (Ketchum). The rationale for the

REDUCE-IT trial was to determine whether VASCEPA would meet the unmet need for an agent that substantially lowers residual cardiovascular risk. Trial Tr. 140:3–8 (Ketchum). Amarin invested hundreds of millions of dollars in this endeavor. Trial Tr. 140:9–15 (Ketchum).

B. Failed Cardiovascular Outcome Trials Involving TG-Lowering Agents

134. The longstanding need for a TG-lowering agent that lowered residual cardiovascular risk was reflected in the numerous clinical trials that were carried out to assess whether TG-lowering agents could lower cardiovascular risk, especially on top of a statin. *See* Trial Tr. 1730:9–20 (Toth Direct); *see also* Trial Tr. 901:13–21 (Heinecke Cross) (discussing failure to develop therapies—fibrates, niacin, other new agents—to raise HDL for cardiovascular risk reduction).

135. Efforts to find a TG-lowering agent—including fibrate products, niacin-based formulations, and various omega-3 fatty acids—that would lower cardiovascular risk began in the 1970s and 1980s, and continued into the 2000s. *See* Trial Tr. 1730:6–14 (Toth Direct). As the 1990s progressed, and statins became a cornerstone of treatment for reducing cardiovascular risk, this interest in reducing cardiovascular risk focused on finding a TG-lowering agent that would significantly reduce cardiovascular risk beyond the risk reduction provided by statin therapy. *See* Trial Tr. 1728:18–1729:9 (Toth Direct) ("[E]ven if a patient is aggressively treated with a statin, if their triglyceride is still high, their risk is substantially higher than a patient who is treated with a statin, but their triglyceride is normal."). But prior to REDUCE-IT, these efforts were met with widespread failure.

136. ***Niacin***. As of March 2008, researchers were investigating whether niacin could reduce risk for cardiovascular events. *See* Trial Tr. 1732:4–7 (Toth Direct); *see also* Trial Tr. 1163:15–1164:21 (Fisher Cross) (discussing the failure of Merck's niacin-based Cordaptive drug). One such trial, the AIM-HIGH study, evaluated the effect of niacin in patients on statin therapy with established cardiovascular disease. *See* Trial Tr. 1732:8–16 (Toth Direct). The AIM-HIGH study failed to show a cardiovascular benefit, and the study was discontinued due to futility. *See id*.

137. Another trial, the HPS2-THRIVE study, evaluated the effect of niacin in high-risk patients against a statin background. *See* Trial Tr. 1732:17–19 (Toth Direct). The HPS2-THRIVE study, too, was negative for its primary composite endpoint and failed to demonstrate efficacy for any individual endpoint. *See* Trial Tr. 1732:17–24 (Toth Direct). Moreover, the study found that the addition of niacin led to heightened risk for pulmonary and urinary tract infections, as well as increased risk for gastrointestinal hemorrhage. *See id*.

138. ***Fibrates.*** As of March 2008, researchers were also investigating the effects of fibrates on cardiovascular disease. *See* Trial Tr. 1731:3–1732:3 (Toth Direct). The ACCORD trial evaluated the effects of fenofibrate on the risk of cardiovascular disease in patients with type 2 diabetes who are on statins. *See* Trial Tr. 1731:3–13 (Toth Direct); *see also* Trial Tr. 1160:13–19 (Fisher Cross). The ACCORD trial was unable to demonstrate incremental benefit with the addition of fenofibrate on top of statin therapy. *See id*. Another trial, the FIELD trial, evaluated the effects of fenofibrate in diabetic patients who were not on statin therapy. *See* Trial Tr. 1731:14–22 (Toth Direct). The FIELD trial also failed to meet its primary composite endpoint. *See id*. Moreover, researchers did not study whether the fibrate gemfibrozil would reduce cardiovascular risk over and above statin therapy because it was deemed unsafe due to its strong interaction with statins, which could precipitate rhabdomyolysis. *See* Trial Tr. 1603:4–14 (Toth Direct) (gemfibrozil interaction with statins), Trial Tr. 1731:23–1732:3 (Toth Direct) (gemfibrozil-statin combination was not studied because "it was deemed to be too unsafe"); *see also* Trial Tr. 1158:19–1159:16 (Fisher Cross).

139. As a result of the failed ACCORD and FIELD trials, fibrates are not used to reduce cardiovascular risk on top of statin therapy. *See* Trial Tr. 1162:2–6 (Fisher Cross) ("Q: [I]t was your testimony at deposition, was it not, that currently fibrates are not used to reduce cardiovascular risks on top of a statin. A: Yes. That was based on the ACCORD and FIELD studies, yes."). Indeed, the American Diabetes Association, in its 2019 Guidelines, recognized that a combination therapy of statins and fibrates "has not been shown to improve atherosclerotic

cardiovascular disease outcomes, and is generally not recommended." *See* PX 162 (ADA 2019 Guidelines) at 11; *see also* Trial Tr. at 1157:13–1158:4 (Fisher Cross).

140. ***Omega-3 mixtures.*** As of March 2008, a number of clinical trials had investigated whether omega-3 fatty acids may provide cardiovascular benefits, but the benefits remained unclear, and questions about the clinical value of omega-3 fatty acids had been highlighted, for example, by a recent meta-analysis by the Cochrane collaboration, which concluded that long chain omega-3 fatty acids "do not have a clear effect on total mortality, combined cardiovascular events, or cancer." *See* PX 848 (Hooper) at 1; *see also* Trial Tr. 1739:18–1742:13 (Toth Direct).

141. To be clear, some clinical trials had reported possible cardio-protective benefits of omega-3 fatty acids. *See* Trial Tr. 1742:18–1743:17 (Toth Direct). These included the GISSI trial—which studied a mixture of EPA and DHA—and the JELIS trial. *See id*. But these trials came in the context of decades of mixed results and were insufficient to lead the medical community to conclude that omega-3 fatty acids were in fact effective to reduce cardiovascular risk. *See, e.g.*, PX 848 (Hooper) at 1 (reporting mixed results based on a review of 48 clinical trials and concluding that "[l]ong chain and shorter chain omega 3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer"); *see also* Trial Tr. at 1742:19–1743:17 (Toth Direct) (discussing GISSI and JELIS), 1739:19–1742:13 (Toth Direct) (discussing Hooper).

142. Ongoing trials as of 2008 included Alpha Omega, DOIT, OMEGA, ORIGIN, SU.FOL.OM3, R&P, AREDS2, and ASCEND. *See* PDX 6-29; Trial Tr. 1732:25-1739:13 (Toth Direct). Prior to the REDUCE-IT trial, all of these trials failed to show a significant cardiovascular benefit, causing the existing doubts about omega-3 fatty acids to grow. *See* PDX 6-29 (table summarizing results and other background information from each of the trials); *see also* Tr. 1736:12–1737:4 (Toth Direct) ("You see in the fourth column primary endpoint, none of the trials were able to achieve statistical significance for their primary composite endpoint."). Of note, these omega-3 trials underway as of March 2008 studied various doses and each studied a composition that contained substantial amounts of DHA. *See* Trial Tr. 1737:8–1739:4 (Toth Direct) ("[P]eople were struggling to find a formulation that worked. They were varying the amount of EPA to DHA.

They were varying the total dosage daily. People were trying to find their way in the dark."); *see also* Trial Tr. 1183:13–16 (Fisher Cross) ("Q: It's fair to say that a variety of trials on a variety of mixtures of EPA and DHA were being conducted in the period up through March 2008, correct. A: Yes.").

143. The exhibit, PDX 6-29, which summarizes the failed omega-3 trials underway as of March 2008 is shown below:

Omega-3 Fatty Acid Cardiovascular Outcome Trials Underway as of March 2008

OM-3 Study (Publication)	Date of Initiation	Omega-3 Formulation Studied	Primary Endpoint Significant	Percentage of Patients on Statins
Alpha Omega (2010)	2002 (PX 0492 at 2)	400 mg EPA-DHA (226 mg EPA + 150 mg DHA) vs. ALA (2 g) vs. EPA-DHA (400 mg) + ALA (2 g) combined	No	85–87%
DOIT (2010)	1997 (PX 0938 at 3)	2.4 g EPA-DHA (49% EPA + 35% DHA)	No	–
OMEGA (2010)	2003 (PX 0936 at 2)	1 g EPA-DHA (460 mg EPA + 380 mg DHA)	No	94–95%
ORIGIN (2012)	2003 (PX 0948 at 5)	1 g EPA-DHA (465 mg EPA + 375 mg DHA)	No	53–55%
SU.FOL.OM3 (2010)	2003 (PX 0956 at 2)	600 mg EPA-DHA (2:1 ratio) vs. folic acid + vitamins B-6 and B-12	No	92%
R & P (2013)	2004 (PX 0949 at 4)	1 g EPA-DHA (ratio ranging from 0.9:1 to 1.5:1)	No	41%
AREDS2 (2014)	2006 (PX0930 at 2)	1 g EPA-DHA (650 mg EPA + 350 mg DHA) vs. lutein + zeaxanthin vs. EPA-DHA + lutein + zeaxanthin	No	44%
ASCEND (2018)	2005 (PX 0961 at 4)	1 g EPA-DHA (460 mg EPA + 380 mg DHA)	No	75%

PDX 6-29

144. The Alpha Omega Trial evaluated the effects of omega-3 fatty acids on the rate of cardiovascular events among patients who have had a myocardial infarction. *See* PX 492 (Kromhout). Patients were enrolled starting in April 2002 and randomly assigned to receive one of four trial margarines: a placebo margarine, a margarine containing approximately 400 mg of EPA-DHA per day (226 mg EPA + 150 mg DHA), a margarine containing 2 g of alpha-linolenic acid (ALA) per day, or a margarine containing a combination of EPA-DHA and ALA. *Id.* at 2. The median TG of the patients receiving EPA-DHA margarines was 144 mg/dL (1.63 mmol/L). *Id.* at 6. 86% of the patients were on lipid-modifying treatment (mainly statins). The primary endpoint of the trial was major cardiovascular events, which comprised fatal and nonfatal cardiovascular disease, the cardiac interventions percutaneous coronary intervention (PCI) and

coronary artery bypass grafting (CABG). *Id.* at 4. After a median follow-up period of 40.8 months, neither EPA-DHA nor ALA significantly reduced the rate of major cardiovascular events. *Id.*

145. The Diet and Omega-3 Intervention Trial (DOIT), whose results were published in October 2010, evaluated the effects of 2.4 g/day of omega-3 fatty acids (49% EPA + 35% DHA) on all-cause mortality in men aged ≥ 50 years. *See* PX 938 (Einvik) at 2–3. Patient randomization began in 1997. *Id*. at 3. The participants' median TG level was 150 mg/dL (1.7 mmol/L). *Id*. at 4. The primary endpoints in the study were changes in carotid intima-media thickness, circulating biomarkers, and peripheral pulse wave propagation. *Id*. All-cause mortality and cardiovascular events were reported as nonprimary endpoints. *Id*. Cardiovascular events were defined as fatal or nonfatal sudden cardiac arrest, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, cerebral stroke, surgery on abdominal aortic aneurysm, or peripheral revascularization procedures. *Id.* After three years, there was no statistically significant reduction in all-cause mortality or cardiovascular events. *Id.* at 2, 5.

146. The OMEGA trial was a prospective, randomized, double-blind, controlled trial including 3,851 patients that evaluated the effects of 1 g/day of omega-3 fatty acids (460 mg EPA + 380 mg DHA) on the rate of sudden cardiac death. *See* PX 936 (Rauch) at 2. Patient randomization began in October 2003. *See id*. The trial defined the primary endpoint of sudden cardiac death as unexpected death resulting from heart disease occurring within 1 hour of the first symptoms or unwitnessed overnight. *Id.* at 3. 94% of the patients received statin therapy. *Id.* at 5. The group of patients receiving omega-3 fatty acids had a mean baseline TG of 121 mg/dL (1.37 mmol/L). *Id*. at 7. After a follow-up period of 1 year, the study failed to support a reduction in the rate of sudden cardiac death. *Id.* at 3, 7.

147. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial evaluated the effects omega-3 fatty acids on the occurrence of cardiovascular events in diabetic patients with recent myocardial infarction or heart failure. *See* PX 948 (Bosch). The ORIGIN trial was a randomized trial with a 2-by-2 factorial design with a 1 g/day capsule containing at least 900 mg of omega-3 fatty acid ethyl esters (465 mg EPA + 375 mg DHA). *Id.* at 1. Randomization

of the study's 12,536 participants began in September 2003, and participants received either 1 g/day of omega-3 fatty acids or placebo. *Id.* at 2, 5. The participants receiving omega-3 fatty acids had a median TG level of 142 mg/dL, and 53% of them were on statin therapy. *Id.* at 5. The primary endpoint was death from cardiovascular causes. After a median follow-up period of 6.2 years, daily supplementation with 1 g/day of omega-3 fatty acids did not reduce the rate of cardiovascular events. *Id.* at 1.

148. The SUpplementation with FOLate, vitamin B6 and B12 and/or OMega-3 fatty acids (SU.FOL.OM3) trial was a double blind randomized, placebo-controlled, secondary prevention trial designed to test the efficacy of folates supplementation (560 μg of 5-methyltetrahydrofolate) in combination with vitamin B-6 (3 mg) and B-12 (20 μg) and/or n-3 PUFA (600 mg of EPA and DHA at a ratio of 2:1) on fatal and non-fatal ischemic cardiovascular disease in a 2×2 factorial design. *See* PX 956 (Blacher) at 2. A total of 2,501 patients with a past history of cardio- or cerebrovascular diseases were recruited between 2003 and 2007. *Id.* The subjects' median baseline TG levels were 114 mg/dL (1.29 mmol/L) in patients with a history of coronary revascularization, 126 mg/dL (1.42 mmol/L) in patients with a history of hard coronary event, and 108 mg/dL (1.22 mmol/L) in patients with no history of coronary event. *Id.* at 3. The primary endpoint was a composite of non-fatal myocardial infarction, non-fatal ischemic stroke, or death from cardiovascular disease. *Id.* at 2. After a mean follow-up period of 4.2 years, the trial did not demonstrate any effects of dietary supplementation with omega-3 fatty acids. *Id.* at 1–2.

149. The Risk and Prevention (R&P) study was a double-blind, placebo-controlled clinical trial designed to evaluate the effects of omega-3 fatty acids in patients with a previous myocardial infarction or heart failure. *See* PX 949 (Roncaglioni). 12,513 patients were randomly assigned to omega-3 fatty acids (1 g EPA-DHA ratio ranging from 0.9:1 to 1.5:1) or placebo beginning in February 2004. *Id.* at 4. 41% of the patients were on statin therapy. *Id.* at 1, 5. At the beginning of the trial, the primary endpoint was the cumulative rate of death, nonfatal myocardial infarction, and non-fatal stroke. *Id.* at 3. After 1 year, the primary endpoint was revised as the composite of time to death from cardiovascular causes or hospital admission for cardiovascular

causes. *Id*. After a median of 5 years of follow-up, daily treatment with omega-3 fatty acids did not reduce cardiovascular mortality and morbidity. *Id.* at 1.

150. The Age-Related Eye Disease Study 2 (AREDS2) was designed to determine whether long chain omega-3 fatty acids reduce the rate of cardiovascular disease. *See* PX 930 (Bonds). Beginning in 2004, 4,203 subjects were randomized to receive 1 g/day of omega-3 fatty acids (350 mg DHA + 650 mg EPA); 10 mg/day of lutein and 2 mg/day of zeaxanthin; omega-3 fatty acids, lutein, and zeaxanthin; or placebo. *Id.* at 1, 4. 44% of the subjects reported taking a statin medication at the start of the study. *Id.* at 3. The primary endpoint was a composite outcome of time to the first event in a category of cardiovascular disease mortality and cardiovascular disease morbidity. *Id*. at 3. After a median follow-up period of 4.8 years, omega-3 fatty acids did not reduce the risk of cardiovascular disease with or without a combination of lutein and zeaxanthin. *Id.* at 1, 3. The results of this trial were published in 2014. *Id*. at 1.

151. The ASCEND trial ("A Study of Cardiovascular Events in Diabetes") evaluated the effects of receiving 1 g/day of omega-3 fatty acid capsules (460 mg EPA + 350 mg DHA) on the risk of serious vascular events in diabetic patients aged ≥ 40 years who did not have evidence of cardiovascular disease. *See* PX 961 (Bowman). From June 2005 through July 2011, a total of 15,480 patients were randomized to receive 1 g/day of omega-3 fatty acid capsules or placebo capsules. *Id*. at 4. 75% of the subjects were on statin therapy. *Id*. at 5. The primary endpoint was the first serious vascular event, which was defined as a composite of nonfatal myocardial infarction or stroke (excluding confirmed intracranial hemorrhage), transient ischemic attack, or vascular death excluding intracranial hemorrhage. *Id*. at 1. The authors specifically acknowledged the great need for an agent to further reduce cardiovascular risk: "Since patients with diabetes have two to three times the risk of cardiovascular disease as the general population, a safe dietary supplement with even a modest protective effect could have a major public health benefit." *Id.* at 2. However, after a follow-up period of 7.4 years, 1 g/day capsules of omega-3 fatty acids did not have a significantly lower incidence of serious vascular events than those who received placebo. *Id*. at 1, 9.

C. ANCHOR

152. ANCHOR was a phase 3, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial to assess the efficacy and safety of AMR101 (VASCEPA) in statin-treated patients at high cardiovascular risk with well-controlled LDL cholesterol and residually high TG levels (≥200 and <500 mg/dL). *See* PX 942 (Ballantyne); Trial Tr. 117:8–120:8 (Ketchum Direct) (discussing the ANCHOR Study).

153. In 2009, Amarin entered into an agreement with FDA relating to a proposed additional indication for VASCEPA—called the Special Protocol Assessment ("SPA") Agreement for the ANCHOR study. Trial Tr. 121:9–122:10 (Ketchum Direct). The agreement provided that Amarin would conduct the requested 12-week lipid endpoint trial—which was ultimately called the ANCHOR trial—to determine whether VASCEPA lowers triglyceride levels in statin-treated patients with well-controlled LDL-C levels and high triglyceride levels (200–499 mg/dL). Trial Tr. 121:20–122:123:18 (Ketchum Direct). In essence, the agreement and related regulatory dialogue provided that if the ANCHOR trial met its study endpoints, and if Amarin enrolled 50% of subjects in the requested cardiovascular outcome trial—which ultimately became the REDUCE-IT study—FDA would grant Amarin an indication to market VASCEPA to treat patients with high triglyceride levels (200–499 mg/dL) on background statin therapy. Trial Tr. 121:20–122:123:18 (Ketchum Direct).

154. The ANCHOR study was conducted at 97 sites in the United States from December 2009 through February 2011 with 702 patients. PX 942 (Ballantyne) at 2–3; Trial Tr. 119:16–19 (Ketchum Direct). The primary endpoint in the trial was the percentage change in triglyceride level from baseline compared to placebo after 12 weeks of treatment. PX 942 (Ballantyne) at 2. Other secondary endpoints included the effect from baseline compared to placebo on other lipid parameters, including LDL-C, non-HDL-C, and apo B. *Id*.

155. When Amarin conducted the ANCHOR trial in 2011, the trial achieved its primary and secondary endpoints, demonstrating a statistically significant reduction in triglyceride levels in the VASCEPA 4 g / day group compared with the placebo (mineral oil) groups (-21.5%) without

increasing LDL-C relatively to placebo, and also demonstrated favorable outcomes with respect to other lipid parameters, including LDL-C (-6.2%), Lp-PLA2 (-19%), non-HDL-C (-13.6%), VLDL-C (-24.4%), and apo B (-9.3%). PX 942 (Ballantyne) at 5–6; Trial Tr. 120:9–121:8 (Ketchum Direct).

156. After obtaining these results, and following Amarin's enrollment of 50% of patients in the REDUCE-IT trial, Amarin in 2013 submitted a supplemental NDA ("sNDA") for its additional proposed indication—seeking approval to market and sell VASCEPA as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, apo B, LDL-C, TC (total cholesterol), and VLDL-C (very low-density lipoprotein cholesterol) in adult patients with mixed dyslipidemia and coronary heart disease or a coronary heart disease risk equivalent. Trial Tr. 123:19–124:10 (Ketchum Direct).

157. But in October 2013, FDA rescinded the ANCHOR SPA, concluding that currently available evidence failed to support the hypothesis that a TG-lowering drug significantly reduces the risk for cardiovascular events among statin-treated patients, and that FDA did not believe that a change in triglyceride levels was sufficient to establish the effectiveness of a drug intended to reduce cardiovascular risk in subjects with serum triglyceride levels below 500 mg/dL. Trial Tr. 124:11–22, 126:11–127:22 (Ketchum Direct). This was based in part on the fact that the cardiovascular outcome trials that had been underway in 2008 when Amarin initially proposed its supplemental indication for VASCEPA—including ACCORD-Lipid and AIM-HIGH—reported negative outcomes. Trial Tr. 126:11–127:22 (Ketchum Direct).

158. It was during the dialogue between Amarin and FDA about the ANCHOR SPA that FDA expressed its view that the Japanese cardiovascular outcome trial known as JELIS had serious methodological flaws and that FDA did not believe that such trial established that EPA provided a cardiovascular benefit on top of statin, even in patients with TGs below 500 mg/dL. Trial Tr. 132:9-133:21, 135:9-11, 135:18-136:12 (Ketchum Direct); PX 990 (FDA Formal Dispute Resolution Request Denial); PX 994 (Declaration of Curtis Rosebraugh). During this time, FDA was "entirely dismissive of JELIS." Trial Tr. 233:25-234:7 (Ketchum Cross).

D. REDUCE-IT

159. REDUCE-IT was a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted to evaluate the effectiveness of VASCEPA as an add-on to statin therapy in reducing the first major cardiovascular event in a high-risk patient population with elevated TGs levels compared to statin therapy alone. PX 1189 (REDUCE-IT CSR) at 7; *see also* Trial Tr. 139:15–140:8 (Ketchum Direct).[8] The rationale for the REDUCE-IT trial was to determine whether VASCEPA would meet the unmet need for an agent that substantially lowers residual cardiovascular risk. Trial Tr. 140:3–8 (Ketchum Direct). Amarin invested several years and more than $300 million in designing and conducting the REDUCE-IT trial. Tr. 140:9–15 (Ketchum Direct).

160. The REDUCE-IT trial enrolled a total of 8,179 patients (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. PX 1189 (REDUCE-IT CSR) at 7, 55, 57, 120. While the enrollment criteria for TG levels was 150 to 499 mg/dL, the REDUCE-IT study included patients with TGs exceeding 500 mg/dL, because after qualifying for the study but before commencing the study medication, their TGs increased to the point where they exceeded 500 mg/dL. PX 1189 (REDUCE-IT CSR) at 195, Tbl. 11-24; Trial Tr. 141:9-143:4 (Ketchum Direct); Trial Tr. 1619:23–1620:18 (Toth Direct). Patients in the REDUCE-IT study also had LDL-C levels of 41 to 100 mg/dL. PX 1189 (REDUCE-IT CSR) at 9, 61–62.

161. The primary endpoint in REDUCE-IT was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. PX 1189 (REDUCE-IT CSR) at 131; Trial Tr. 1616:18–1617:9 (Toth Direct). The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. PX 1189 (REDUCE-IT CSR) at 134; Trial Tr. 1617:10–17 (Toth Direct).

[8] The results of REDUCE-IT are set forth in the Clinical Study Report. PX 1189 (REDUCE-IT CSR). The results were also published in the *New England Journal of Medicine*. *See* PX 272 (Bhatt).

162. REDUCE-IT showed that the use of VASCEPA results in a remarkable degree of cardiovascular risk reduction, over and above the risk reduction provided by statin therapy, in patients whose LDL-C levels were well-controlled—with an LDL-C upper limit of 100 mg/dL. PX 1189 (REDUCE-IT CSR) at 137, Fig 11-3; Trial Tr. 1617:18–1619:22, 1625:2–10 (Toth Direct). Compared to placebo, VASCEPA showed

- a statistically significant 25% risk reduction in the primary composite end point;
- a statistically significant 26% risk reduction in the key secondary endpoint;
- a statistically significant 20% reduction in the risk of cardiovascular death;
- a statistically significant 31% in nonfatal myocardial infarction
- a statistically significant 29% reduction in nonfatal stroke;
- a statistically significant 33% reduction in coronary revascularization; and
- a statistically significant 32% reduction in hospitalization for unstable angina.

PX 1189 (REDUCE-IT CSR) at 137, Fig. 11-3; Trial Tr. 1617:18–1619:22 (Toth Direct).

163. The REDUCE-IT results established that VASCEPA lowers cardiovascular risk in patients with very high TGs. PX 1189 (REDUCE-IT CSR) at 195, Tbl. 11-24; Trial Tr. 1619:23–1622:16 (Toth Direct). The REDUCE-IT study included a tertile analysis, showing the cardiovascular risk reduction from in patients with the lowest baseline TG level range (81 to 190 mg/dL), the middle baseline TG level range (190 to 250 mg/dL), and the highest baseline TG level range (250 to 1,401 mg/dL). PX 1189 (REDUCE-IT CSR) at 195, Tbl 11-24; Trial Tr. 1619:23–1622:16 (Toth Direct). The patients in the highest tertile—which included patients with baseline TG levels exceeding 500 mg/dL—reported a 32.5% cardiovascular risk reduction, which was nominally greater than, and not statistically different from, the patients in the other tertiles with lower baseline TG levels. PX 1189 (REDUCE-IT CSR) at 195, Tbl. 11-24; Trial Tr. 1619:23–1622:16 (Toth Direct). This analysis demonstrates that patients taking VASCEPA experience cardiovascular benefits regardless of TG level, including in patients with severe hypertriglyceridemia (exceeding 500 mg/dL). PX 1189 (REDUCE-IT CSR) at 195, Tbl 11-24; Trial Tr. 1619:23–1622:16 (Toth Direct).

164. After the MARINE trial, there was no longer a reason to be concerned that LDL-C increases in patients with severe hypertriglyceridemia could negate the cardiovascular benefits observed in patients with lower TGs. Trial Tr. 1622:24–1623:8 (Toth Direct). Before MARINE, and as of March 2008, that would have been a major concern, but MARINE showed that that EPA lowers TGs in patients with severe hypertriglyceridemia without increasing LDL-C. *See supr*a ¶¶ 72–74. "In addition, the significantly lower risk of major adverse cardiovascular events with [VASCEPA] than with placebo appeared to occur irrespective of the attained triglyceride level at one year whether it's greater than or equal to 150 or less than 150 milligrams per deciliter, which suggests that the cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level." PX 272 (Bhatt) at 10; Trial Tr. 1623:14–1624:20 (Toth Direct). These facts indicate that cardiovascular benefits of VASCEPA accrue regardless of baseline TG level, and that patients derive cardiovascular benefit from VASCEPA even if they do not attain a normal level of triglycerides. Trial Tr. 1624:15–20 (Toth Direct).

165. In view of these facts, the REDUCE-IT trial has established that VASCEPA reduces cardiovascular risk on top of statin in patients with very high TGs—a conclusion that FDA shares. Trial Tr. 1619:23–1625:21 (Toth Direct); Trial Tr. 849:21–24 (Heinecke Cross) ("Q. So FDA has determined, based on REDUCE-IT, that the effect of EPA on cardiovascular risk in patients with severe hypertriglyceridemia has been determined? A. I'll accept that as being correct.").

166. Based on the results of the REDUCE-IT study, Amarin submitted a supplemental New Drug Application in March 2019. Trial Tr. 150:10–14 (Ketchum Direct). After reviewing the results of the REDUCE-IT study, FDA in December 2019 expanded the approved use of VASCEPA to include reduction in cardiovascular risk in patients with TG levels over 150 mg/dL, including persons with very high TGs. *See* PX 1186 (VASCEPA Label 2019) at 1; PX 1185 (FDA Press Release). In addition to the severe-hypertriglyceridemia indication first approved in July 2012, VASCEPA is now also indicated

> as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.

See PX 1186 (VASCEPA Label 2019) at 1.

167. In approving the expanded indication, FDA removed the Limitation of Use that stated "[t]he effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined," thus recognizing VASCEPA's cardiovascular benefit in patients with very high TGs. *Compare* PX 940 (VASCEPA Label 2017) at 2 *with* PX 1186 (VASCEPA Label 2019) at 2; *see also* Trial Tr. 848:21–849:24 (Heinecke Cross); Trial Tr. 1114:23–11154 (Fisher Cross).

168. Now, "VASCEPA is the first FDA-approved drug to reduce cardiovascular risk among patients with elevated triglyceride levels as an add-on to maximally tolerated statin therapy." PX 1185 (FDA Press Release) at 1; *see also* Trial Tr. 1625:11–21 (Toth Direct). VASCEPA is also the only drug approved for treatment of severe hypertriglyceridemia that has also been shown to provide cardiovascular benefit to these patients. Trial Tr. 1625:11–21 (Toth Direct).

169. The results from the REDUCE-IT trial will have tremendous real-world value in the practice of medicine, including the treatment of severe hypertriglyceridemia. Trial Tr. 1625:11–21 (Toth Direct). Doctors can now make progress in reducing cardiovascular risk in patients with severe hypertriglyceridemia at the same time they are addressing pancreatitis risk.

170. The results of REDUCE-IT have been met with widespread enthusiasm and surprise. Trial Tr. 1625:22–1633:5 (Toth Direct); PX 959 (Kastelein); PX 875 (Fidler) PX 714 (Key Opinion Leaders Conference Call); PX 952 (O'Connor); PX 902 (Hackett). Some clinicians have considered it the most significant advance since statin therapy, and others call it "practice-changing." Trial Tr. 161:6–11 (Ketchum Direct). Expressions of enthusiasm and surprise include:

- An editorial in The New England Journal of Medicine from Dr. John Kastelein of the Academic Medical Center, University of Amsterdam, stating that "[w]e welcome these results with surprise, speculation, and hope. Most surprising was the difference between the results of REDUCE-IT and those of many previous trials of omega-3 fatty acids . . . . [A]fter a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events." *See* PX 959 (Kastelein) at 1–2; Trial Tr. 1626:6–1628:18 (Toth Direct).

- A statement from Dr. Norman Lepor, a cardiologist at Cedars-Sinai Heart Institute and professor of medicine at UCLA, that "the results will impact how I treat patients starting tomorrow." *See* PX 875 (Fidler) at 2, 3; Trial Tr. 1628:19–1630:10 (Toth Direct).

- A statement from Dr. Michael J. Blaha, the Director of Clinical Research at the Ciccarone Center for the Prevention of Heart Disease at Johns Hopkins Medical School, that "I'm very surprised by the magnitude of the results, which quite frankly are large . . . A lot of people are legitimately surprised by this.'"). *See* PX 952 (O'Connor) at 1; Trial Tr. 1630:19–1633:5 (Toth Direct).

- A statement from that Prakash C. Deedwania, MD, Chief of the Cardiology Division at the Veterans Affairs Medical Center/University of California San Francisco Program in Fresno, that "REDUCE-IT is a phenomenal trial and a game changer because it has shown for the first time that triglyceride reduction with an appropriate therapy – in this case icosapent ethyl – when used in appropriate doses can make a significant difference."). *See* PX 902 (Hackett) at 1; Trial Tr. 1630:19–1633:5 (Toth Direct)).

- A statement from Dr. Michael Shapiro, Cardiologist at Oregon Health Science University in Portland, Oregon that "most people in this field would look at this as a home run. And really view this as being an inflection point in our ability to manage (atherosclerotic) cardiovascular disease. We have a new option that impacts cardiovascular outcomes to a greater extent than just throwing on more LDL cholesterol lowering drugs. . . . So now we have a new option for patients in this category who also happen to have elevated triglycerides where you're going to get more bang for your buck by using kind of a[n] orthogonal therapy.") *See* PX 714 (Key Opinion Leaders Call) at 3, 10; Trial Tr. 1630:19–1633:5 (Toth Direct).

171. Moreover, numerous national and international groups have embraced the REDUCE-IT results, recognizing VASCEPA as an add-on to statin therapy and for cardiovascular risk reduction—including the American Diabetes Association, the National Lipid Association, The European Society of Cardiology, and the European Atherosclerosis Society, among others. Trial Tr. 161:6–22 (Ketchum Direct).

VII. VASCEPA'S APPROVED PRESCRIBING INFORMATION AFTER REDUCE-IT

172. In general, prescription drug labels are referred to alternatively as the label, labeling, prescribing information, and/or package insert. Trial Tr. 1324:13–18 (Peck Direct).

173. The Indications and Usage section of the VASCEPA label states that "VASCEPA (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." PX 1186 (VASCEPA Label 2019) at 2.[9]

174. The Indications and Usage section thus instructs clinicians that VASCEPA is approved (*i.e.*, safe and effective) for use in combination with diet to reduce TGs in adult patients with severe hypertriglyceridemia—without concurrent administration of any other medication. Trial Tr. 1375:16–19 (Peck Cross); Trial Tr. 1352:12–20 (Peck Direct).

175. The Indications and Usage section of the VASCEPA label does not specify a duration of use. PX 1186 (VASCEPA 2019 Label) at 2. The absence of a limitation on duration tells clinicians that FDA has determined that there are no safety or efficacy concerns that require limiting the duration of use of VASCEPA. Given the lack of any duration of use combined with the indication to treat a chronic condition, the Indications and Usage section instructs clinicians to prescribe VASCEPA long-term. Trial Tr. 1373:19–1374:1, 1338:8–1339:6 (Peck Cross).

176. Prior to December 2019, VASCEPA's labeling also included a "Limitation of Use" advising clinicians that VASCEPA's effect on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia had not been determined. *See* PX 940 (VASCEPA Label 2017) at 2. That "Limitation of Use" was dropped when FDA approved VASCEPA's new indication for cardiovascular risk-reduction. *See* PX 1186 (VASCEPA Label 2019) at 2.

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[9] The Indications and Usage section of VASCEPA's current labeling adds a second approved indication: "as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." PX1186 (VASCEPA Label 2019) at 2. This indication, referred to during trial as the "REDUCE-IT indication," is carved out of Defendants' labels.

177. The Dosage and Administration section of the VASCEPA label includes two sub-headings. The first reads, "2.1 Prior to Initiation of VACEPA." *Id*. Under this heading, the label advises clinicians to "[a]ssess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate." *Id.* This subheading also advises clinicians that "[p]atients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA." *Id.*

178. The second sub-heading is "2.2 Dosage and Administration." Here, the label states that "[t]he daily dose of VASCEPA is 4 grams per day taken as either: four 0.5 gram capsules twice daily with food; or as two 1 gram capsules twice daily with food." *Id.* The label also instructs clinicians to "[a]dvise patients to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA." *Id*; *see also* Trial Tr. 68:24–69:16 (Ketchum Direct).

179. The Dosage and Administration section in VASCEPA's labeling does not specify a duration of use. *See* PX 1186 (VASCEPA Label 2019) at 2. The absence of a duration limitation in this section conveys that VASCEPA's benefit does not stop after a particular duration of treatment. Trial Tr. 1343:5–9 (Peck Direct). This means that Vascepa was approved for long-term use to reduce TGs and maintain that reduction. Trial Tr. 1344:3–14 (Peck Direct).

180. The Dosage and Administration section in VASCEPA's labeling does not recommend use of any concomitant medication. *See* PX 1186 (VASCEPA Label 2019) at 2. This conveys that FDA approved Vascepa as a monotherapy to reduce TGs in adult patients with severe hypertriglyceridemia (Trial Tr. 1355:7–10 (Peck Direct)), and that FDA does not believe that the safety or effectiveness of Vascepa depends on concurrent administration of another medication. Trial Tr. 1354:20–25 (Peck Direct); Trial Tr. 67:7–12 (Ketchum Direct).

181. The Dosage Forms and Strength section of the VASCEPA label informs clinicians that VASCEPA is available as a 1-gram or 0.5-gram soft-gelatin capsule. PX 1186 (VASCEPA Label 2019) at 2; Trial Tr. 67:13–68:6 (Ketchum Direct).

182. The Contraindications section of the VASCEPA label states that VASCEPA is contraindicated only in patients with known hypersensitivity to VASCEPA or any of its components. PX 1186 (VASCEPA Label 2019) at 2.

183. The Warnings and Precautions section of a drug label is intended to describe serious or otherwise clinically significant adverse reactions and safety hazards of which clinicians need to be aware before prescribing the drug. *See* 21 C.F.R. § 201.57(c)(6); Trial Tr. 358:10–15 (Budoff Direct). The Warnings and Precautions section of the VASCEPA label states that VASCEPA was associated with an increased risk of atrial fibrillation or atrial flutter and an increased risk of bleeding. PX 1186 (VASCEPA Label 2019) at 2–3. It also cautions against the use of VASCEPA in patients with known hypersensitivity to fish and/or shellfish. *Id.*

184. Unlike Lovaza's labeling, the Warnings and Precautions section of the VASCEPA labeling does not warn of a potential increase in LDL-C levels. Trial Tr. 407:7–25 (Budoff Direct); *Compare* PX 566/DX 1578 (Lovaza 2007 Label) at 1, *with* PX 1186 (VASCEPA Label 2019) at 2–3; *see also supra* ¶¶ 34, 38, 52.

185. The Description section of the VASCEPA label informs clinicians that the active ingredient in VASCEPA is "[i]cosapent ethyl," which "is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA)," and that "[e]ach VASCEPA capsule contains . . . 1 gram of icosapent ethyl (in a 1 gram capsule)." PX 1186 (VASCEPA Label 2019) at 6; Trial Tr. 68:7–23 (Ketchum Direct). This section also states that VASCEPA is for "oral use." PX 1186 (VASCEPA Label 2019) at 6; *see also* Trial Tr. 418:2–5 (Budoff Direct).

186. The Nonclinical Toxicology section of a prescription drug label discloses the results of studies conducted on rodents, or other non-human subjects. "It's generally expected that a carcinogenicity study be conducted in two rodent species to support marketing approval of a new chemical entity for a chronic use indication." Trial Tr. 110:14–17 (Ketchum Direct). Amarin performed two such studies, and their results are reflected in the Nonclinical Toxicology section of the VASCEPA label. Trial Tr. 111:11–20 (Ketchum Direct); PX 1186 (VASCEPA Label 2019) at 8. Both rodent studies, the rat study described in the first paragraph and the mouse study

described in the second paragraph of the section, "supported there was no carcinogenic potential of icosapent ethyl." Trial Tr. 112:1–7 (Ketchum Direct).

187. The Clinical Studies section of the VASCEPA label, sub-heading 14.2, describes the design and results of the MARINE study, the primary study that established VASCEPA's effectiveness at reducing triglycerides in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. *See* PX 1186 (VASCEPA 2019 Label) at 10–11.[10]

188. First, the Clinical Studies section "14.2 Severe Hypertriglyceridemia" in each label begins by summarizing the major design characteristics of the MARINE study. Section 14.2 states:

> The effects of Vascepa 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on Vascepa, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (76%). The mean age was 53 years and the mean body mass index was 31 kg/m^2. Twenty-five percent of patients were on concomitant statin therapy, 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL.

PX 1186 (VASCEPA 2019 Label) at 10–11.

189. Next, Section 14.2 of the Clinical Studies Section includes a table summarizing the "major lipoprotein lipid parameters for the groups receiving Vascepa or placebo" and beneath the table is a brief summary of the conclusions. PX 1186 (VASCEPA Label 2019) at 11, Tbl. 2.

[10] The 2019 label added to the Clinical Studies section the design and results of the REDUCE-IT study, under sub-heading 14.1. PX 1186 (VASCEPA Label 2019) at 8–10. This portion of the Clinical Studies section is carved out of Defendants' labels.

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA or placebo are shown in Table 2.

Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

	VASCEPA 4 g/day N=76		Placebo N=75		Difference (95% Confidence
Parameter	Baseline	% Change	Baseline	% Change	Interval)
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9**(-14, -3)

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test
*p-value < 0.001 (primary efficacy endpoint)
**p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

VASCEPA 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo.

Beneath Table 2, there is a paragraph highlighting key results of the MARINE trial. *Id.* Amarin included the statements below Table 2 because it wanted to "apprise[]" "healthcare professionals" and "draw the healthcare professional's attention" to the "key information from that pivotal trial." Trial Tr. 98:8–99:14 (Ketchum Direct).

190. The Patient Counseling Information section of the VASCEPA label instructs clinicians to "[a]dvise the patient to read the FDA-approved patient labeling before starting VASCEPA (Patient Information)," and then lists five topics for discussion with patients: (1) the potential increased risk for atrial fibrillation or atrial flutter; (2) the potential for allergic reactions in patients with hypersensitivity to fish and/or shellfish; (3) the increased risk of bleeding, particularly in patients receiving other antithrombotic agents; (4) the need to swallow VASCEPA capsules whole, and (5) and the need to take VASCEPA as prescribed. *See* PX 1186 (VASCEPA 2019 Label) at 11–12.

191. The Patient Information page at the end of the label is a handout that patients may take with them. It reiterates much of the same information included in the label itself, but in lay

language. Trial Tr. 359:11–24 (Budoff Direct); *see also* Mathers Dep. Tr. 126:2–5, 7–20 (explaining how the Patient Information page distills information into user-friendly language).

192. Among other things, the VASCEPA Patient Information sheet instructs patients to "[t]ake VASCEPA exactly as your doctor tells you to take it" and to "not change your dose or stop taking VASCEPA without talking to your doctor." PX 1186 (VASCEPA Label 2019) at 13–14. The Patient Information sheet also instructs patients to "[t]ake VASCEPA capsules whole" and to "not break, crush, dissolve, or chew VASCEPA capsules before swallowing." *Id.* The Patient Information sheet also advises that "your doctor may do blood tests to check your triglyceride and other lipid levels while you take VASCEPA." *Id.*

VIII. DEFENDANTS' PROPOSED GENERIC DRUGS

A. Abbreviated New Drug Applications

193. A company wishing to market a generic copy of a drug previously approved by FDA—known as the "Reference Listed Drug" ("RLD")—may follow a truncated approval process by filing an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. § 355(j).

194. Unlike an NDA applicant, an ANDA applicant is not required to include safety and effectiveness data. Instead, the ANDA applicant is permitted to rely on the prior approval of the RLD—in essence, piggybacking on the NDA application and safety and effectiveness conclusions. 21 U.S.C. § 355(j). An ANDA applicant may not establish new conditions of use for the proposed drug product. Instead, an ANDA applicant may seek approval only for conditions of use that previously have been approved for the RLD. 21 U.S.C. § 355(j)(2)(A)(i).

195. An ANDA applicant must show that its proposed product is the "same as" the RLD, meaning it is "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use," though the applicant may omit "conditions of use" for which FDA cannot grant approval "because of exclusivity or an existing patent." 21 C.F.R. § 314.92(a)(1).

196. To obtain FDA approval under 21 C.F.R. § 314.105(d), an ANDA applicant in Defendants' position must show, among other things, that

- The methods, facilities, controls used for manufacture, processing, and packing of the proposed drug product are adequate to "preserve its identity, strength, quality, and purity," 21 C.F.R. § 314.127(a)(1);

- FDA has already approved each proposed condition of use for the RLD, *id.* § 314.127(a)(2);

- The active ingredient(s) in the proposed ANDA product is (are) the same as the RLD, *id.* § 314.127(a)(3);

- The route of administration, dosage form, and strength for the proposed drug product are the same as for the RLD, *id.* § 314.127(a)(4);

- The proposed drug product is bioequivalent to the RLD, *id.* § 314.127(a)(6); and

- The labeling proposed for the drug is "the same as the labeling approved for the [RLD]," except for changes required because the proposed drug product and the RLD "are produced or distributed by different manufacturers or because the [RLD's] labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the [RLD] for all remaining, nonprotected conditions of use," *id.* § 314.127(a)(7).

B. Hikma's ANDA No. 209457

197. On July 26, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. submitted to FDA ANDA No. 209457 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of VASCEPA (icosapent ethyl) 1 g capsules. Joint Stipulations of Fact ¶ 183 (ECF No. 324).

198. VASCEPA is the RLD for ANDA No. 209457. Joint Stipulations of Fact ¶ 210 (ECF No. 324).

199. In a letter dated September 21, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. notified Amarin pursuant to 21 U.S.C. § 355(j)(2)(B) that they had submitted ANDA No. 209457 to FDA along with paragraph IV certifications for all patents listed in the Orange Book, including the Asserted Patents. Joint Stipulations of Fact ¶ 185 (ECF No. 324); PX 1140 (Roxane Paragraph IV Letter (Sept. 21, 2016)) at 2.

200. Thus, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. had knowledge of the Asserted Patents when they filed ANDA No. 209457. *See* PX 1156 (Roxane Paragraph IV Certification) at 1.

201. On October 31, 2016, Amarin filed a complaint for patent infringement against Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. in this Court, alleging that their submission of ANDA No. 209457 to obtain FDA's approval for a generic version of the 1 g strength of VASCEPA before the expiration of the Asserted Patents constitutes infringement of those patents under 35 U.S.C. § 271(e)(2), and that, if Hikma Pharmaceuticals and Roxane Laboratories, Inc. were to commercially use, offer for sale, or sell their generic version of VASCEPA, or induce or contribute to such conduct, they would further infringe the Asserted Patents under 35 U.S.C. § 271(a), (b), and/or (c). The Court designated the action as Case No. 2:16-cv-02525. *See* Compl. for Patent Infringement (ECF No. 1).

202. On or about December 8, 2016, Roxane Laboratories, Inc. transferred ANDA No. 209457 to West-Ward Pharmaceuticals International Limited. Joint Stipulations of Fact ¶ 186 (ECF No. 324).

203. On or about December 8, 2016, West-Ward Pharmaceuticals International Limited appointed West-Ward Pharmaceuticals Corp. as its agent for purposes of communication with FDA regarding ANDA No. 209457. Joint Stipulations of Fact ¶ 187 (ECF No. 324).

204. On February 24, 2017, the Court entered an order substituting West-Ward Pharmaceuticals International Limited and West-Ward Pharmaceuticals Corp. for Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. as Defendants in this action. *See* Stipulation and Order Substituting West-Ward Pharm. Corp. and West-Ward Pharm. Int'l Ltd. as Defs. and Counter-Claim Pls. (ECF No. 52).

205. West-Ward Pharmaceuticals Corp. subsequently changed its name to Hikma Pharmaceuticals USA Inc. Joint Stipulations of Fact ¶ 190 (ECF No. 324).

206. On August 2, 2018, the Court entered an order substituting Hikma Pharmaceuticals USA Inc. for West-Ward Pharmaceuticals Corp. as a Defendant in this action. *See* Unopposed

Mot. and Order to Substitute Hikma Pharm. USA Inc. for West-Ward Pharm. Corp. (ECF No. 132).

207. West-Ward Pharmaceuticals International Limited subsequently changed its name to Hikma Pharmaceuticals International Limited. Joint Stipulations of Fact ¶ 189 (ECF No. 324).

208. On February 15, 2019, the Court entered an order substituting Hikma Pharmaceuticals International Limited for West-Ward Pharmaceuticals International Limited as a Defendant in this action. *See* Unopposed Mot. and Order to Substitute Hikma Pharm. Int'l Ltd. for West-Ward Pharm. Int'l Ltd. (ECF No. 185).

209. On or about July 8, 2019, Hikma Pharmaceuticals International Limited transferred ANDA No. 209457 to Hikma Pharmaceuticals USA Inc. Hikma Pharmaceuticals USA Inc. is now the owner of ANDA No. 209457. Joint Stipulations of Fact ¶ 191 (ECF No. 324).

C. DRL's ANDA No. 209499

210. On July 26, 2016, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA ANDA No. 209499 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of VASCEPA (icosapent ethyl) 1 gram capsules. Joint Stipulations of Fact ¶ 193 (ECF No. 324).

211. VASCEPA is the RLD for ANDA No. 209499. Joint Stipulations of Fact ¶ 222 (ECF No. 324).

212. In a letter dated September 22, 2016, DRL notified Amarin pursuant to 21 U.S.C. § 355(j)(2)(B) that it had submitted ANDA No. 209499 to FDA along with paragraph IV certifications for all patents listed in the Orange Book, including the Asserted Patents. Joint Stipulations of Fact ¶ 195 (ECF No. 324); PX 1142 (Dr. Reddy's Paragraph IV Letter (1 g) (Sept. 22, 2016)) at 2.

213. Thus, DRL had knowledge of the Asserted Patents when it filed ANDA No. 209499. *See* PX 1157 (DRL Paragraph IV Certification) at 1–2.

214. On November 4, 2016, Amarin filed a complaint for patent infringement against DRL in this Court, alleging that DRL's submission of ANDA No. 209499 to obtain FDA's

approval for a generic version of the 1 g strength of VASCEPA before the expiration of the Asserted Patents constitutes infringement of those patents under 35 U.S.C. § 271(e)(2), and that, if DRL were to commercially use, offer for sale, or sell its generic version of VASCEPA, or induce or contribute to such conduct, it would further infringe the Asserted Patents under 35 U.S.C. § 271(a), (b), and/or (c). The Court designated the action as Case No. 2:16-cv-02562. *See* Compl. for Patent Infringement, *Amarin Pharm. Inc. v. Dr. Reddy's Labs. Inc.*, Case No. 2:16-cv-02562 (D. Nev. Nov. 4, 2016) ECF No. 1.

215. On January 10, 2017, the Court consolidated the DRL 1 g infringement action, Case No. 2:16-cv-02562, with the Hikma 1 g infringement action, Case No. 2:16-cv-02525, with the latter case serving as the lead case. *See* Consolidation Order (ECF No. 30); Consolidation Order, *Amarin Pharm. Inc. v. Dr. Reddy's Labs. Inc.*, Case No. 2:16-cv-02562, (D. Nev. Jan. 10, 2017) ECF No. 28.

216. On or about July 11, 2018, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a supplement to ANDA No. 209499 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of VASCEPA (icosapent ethyl) 500 mg capsules. Joint Stipulations of Fact ¶ 197 (ECF No. 324).

217. In a letter dated July 11, 2018, DRL notified Amarin pursuant to 21 U.S.C. § 355(j)(2)(B) that it had submitted the 500 mg supplement to ANDA No. 209499 to FDA along with paragraph IV certifications for all patents listed in the Orange Book, including the '728, '715, '677, '652, and '929 patents. Joint Stipulations of Facts ¶ 198 (ECF No. 324).

218. Thus, DRL had knowledge of the '728, '715, ' 677, '652, and '929 Patents when it filed the 500 mg supplement to ANDA No. 209499. *See* PX 1141 (Dr. Reddy's Paragraph IV Letter (500 mg) (July 11, 2018)).

219. On August 24, 2018, Amarin filed a Complaint for patent infringement against DRL in this Court, alleging that DRL's submission of a supplement to ANDA No. 209499 seeking FDA approval to market a generic version of the 500 mg strength of VASCEPA before the

expiration of several patents, including the '728, '715, '677, '652, and '929 Patents, constitutes infringement of those patents under 35 U.S.C. § 271(e)(2), and that, if DRL were to commercially use, offer for sale, or sell its generic version of VASCEPA, or induce or contribute to such conduct, it would further infringe these patents under 35 U.S.C. § 271(a), (b), and/or (c). The Court designated that action as Case No. 2:18-cv-01596. *See* Compl. for Patent Infringement, *Amarin Pharm. Inc. v. Dr. Reddy's Labs. Inc.*, Case No. 2:18-cv-01596 (D. Nev. Aug. 24, 2018) (ECF No. 1).

220. Amarin and DRL have stipulated that the final judgment in the consolidated 1 g infringement actions will bind Amarin and DRL as though that judgment were also made in the 500 mg infringement action. *See* Joint Stipulation and Order Regarding Agreement to Be Bound By Judgment in Related ANDA Litig., *Amarin Pharm. Inc. v. Dr. Reddy's Labs. Inc.*, Case No. 2:18-cv-01596 (D. Nev. Oct. 19, 2018) (ECF No. 27).

D. Defendants' ANDA Products

221. In their respective ANDAs, Hikma and DRL seek FDA approval to market generic versions of VASCEPA 1 g capsules as Icosapent Ethyl Capsules, 1 gram (individually, "Hikma's ANDA Product" and "DRL's ANDA Product") (collectively, "Defendants' ANDA Products"). Joint Stipulations of Fact ¶¶ 213, 225 (ECF No. 324).

222. Defendants specifically seek approval to market their ANDA Products for use "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia"—the indication for which FDA first approved VASCEPA in July 2012. Joint Stipulations of Fact ¶¶ 212, 224 (ECF No. 324).

223. The active pharmaceutical ingredient in Defendants' ANDA Products is icosapent ethyl, which is the same active ingredient as in VASCEPA. *See* Joint Stipulations of Fact ¶¶ 215, 227 (ECF No. 324); PX 1203 (Hikma 2019 Proposed Label) at 10; PX 1209 (DRL 2020 Proposed Label) at 12; PX 1186 (VASCEPA Label 2019) at 6, 14; Cady Dep. 71:21–72:2 (Oct. 26, 2018).

224. Defendants have stipulated that the pharmaceutical composition in their ANDA Products—*i.e.* the drug substance inside their icosapent ethyl capsules—will be comprised of 96%

or more ethyl EPA and less than 3–4% DHA or its esters, as required by the Asserted Claims. Joint Stipulations of Fact ¶¶ 217–221, 229–234 (ECF No. 324).

225. If approved, Defendants' ANDA Products will be bioequivalent to VASCEPA. Joint Stipulations of Fact ¶¶ 211, 223 (ECF No. 324).

226. Like VASCEPA, Defendants' ANDA Products, if approved, will be marketed as capsules that are intended to be administered orally and swallowed whole. PX 1203 (Hikma 2019 Proposed Label) at 2, 5; PX 1209 (DRL 2020 Proposed Label) at 1–2, 5; PX 1186 (VASCEPA 2019 Label) at 2, 6.

227. Like VASCEPA, the daily dose of Defendants' ANDA Products, if approved, will be 4 g per day, taken as two 1 g capsules twice daily with food. Joint Stipulations of Fact ¶¶ 214, 226 (ECF No. 324).

228. At trial, experts on both sides agreed that there were no meaningful differences between the VASCEPA label and Defendants' proposed labels that would impact their opinions. Trial Tr. 356:12–20 (Budoff Direct); Trial Tr. 601:14–18 (Sheinberg Direct); Trial Tr. 649:5–11 (Sheinberg Cross); Trial Tr. 1334:11–19 (Peck Direct); Mathers Dep. 33:8–14, 34:3–10, 16–20.

IX. TRIAL

A. Live Testimony

229. **Matthew Budoff M.D. (Plaintiffs' Expert).** Dr. Budoff was admitted as an expert in the clinical treatment of patients with lipid disorders, including severe hypertriglyceridemia, and as an expert in cardiology. Trial Tr. 323:11–14 (Budoff Direct**)**.

230. Dr. Budoff has practiced in the field of preventive cardiology for over twenty years. Trial Tr. 309:25–311:9 (Budoff Direct). He maintains an active clinical practice where he treats approximately 200 patients per month, many of whom have elevated triglycerides and LDL-C, and are at increased risk for cardiovascular events. He also directly supervises cardiology fellows in their treatment of several hundred patients per week. Trial Tr. 320:1–322:4 (Budoff Direct).

231. Dr. Budoff is currently the Program Director at the Lundquist Institute for Biomedical Innovation, affiliated with the David Geffen School of Medicine at the University of

California, Los Angeles (UCLA) and Harbor UCLA Medical Center. In addition to serving as Program Director, Dr. Budoff is employed as a researcher and Professor of Medicine. As a Professor of Medicine, Dr. Budoff instructs and supervises current medical students, interns, residents, and cardiology fellows. This includes teaching courses, giving lectures, and supervising the treatment of patients. Trial Tr. 308:24–309:15 (Budoff Direct).

232. Outside of his obligations as a Professor of Medicine, Dr. Budoff regularly lectures practicing clinicians at large symposia and national and international meetings on the treatment of various aspects of preventive cardiovascular health, such as lipid abnormalities and cardiac imaging. Trial Tr. 314:8–22 (Budoff Direct).

233. In his capacity as a researcher, Dr. Budoff performs and supervises clinical studies, having supervised over 100 clinical studies as a principal investigator and approximately one dozen as a national principal investigator. As the principal investigator of a clinical study, Dr. Budoff is responsible for all aspects of the study including design of the study (how many patients, how to follow up, what the end points will be), execution of the study, and publication of study results. For example, Dr. Budoff was an investigator on two studies involving VASCEPA, the EVAPORATE and REDUCE-IT trials. Trial Tr. 315:12–318:5 (Budoff Direct).

234. Dr. Budoff has received significant recognition for his work. *See* PX 1161 (Budoff CV) at 3–6. He was appointed to serve as the Endowed Chair of Preventive Cardiology at the Lundquist Institute for Biomedical Innovation and has previously been appointed to positions including Foundation Board Member of the American College of Cardiology, Chair of the Annual Scientific Meeting Committee, and the president of societies including the Society of Cardiovascular Computed Tomography and the Society of Atherosclerosis Imaging and Prevention. *Id.* at 1–3. Most recently, Dr. Budoff was named to the World's Most Influential Scientific Researchers in 2018 and 2019, America's Most Honored Professionals in 2019, and was inducted into the World Academy of Sciences in 2019. *Id.* at 4.

235. Dr. Budoff testified about the basic scientific principles behind severe hypertriglyceridemia, how clinicians typically treated the condition prior to the development of

VASCEPA, and how VASCEPA greatly improved the treatment options available. Dr. Budoff walked through the VASCEPA prescribing information and explained the meaning of important sections to a prescribing clinician. Applying this information, Dr. Budoff then analyzed the VASCEPA label in light of Amarin's Asserted Claims, and testified that, from the perspective of a clinician, Defendants' proposed products will induce infringement of the Asserted Claims. Trial Tr. 308:8–439:21 (Budoff Direct) (complete direct examination of Dr. Budoff).

236. In addition to performing his research and teaching obligations on behalf of academic institutions, Dr. Budoff also performs similar work on behalf of various pharmaceutical companies. Trial Tr. 529:7–11 (Budoff Cross). Over the last several years, Dr. Budoff has worked with Amarin on various consulting work outside the context of this litigation, for which he received payment. Trial Tr. 528:22–531:3 (Budoff Cross). When questioned about payments from Amarin during cross examination, Dr. Budoff testified that he has received certain payments from Amarin (*e.g.*, "I'm definitely responsible for receiving the consulting fees of $33,000 and the honorarium of $27,000), but explained that other payments represent payments to his employer, the Lundquist Institute, rather than him personally (*e.g.*, "a research grant of $900,000 related to the EVAPORATE study" which "goes to [his] institution, not to [him]"). Trial Tr. 533:15–535:10 (Budoff Cross). Over a week after Dr. Budoff testified—and during the cross-examination of a different Amarin witness, Dr. Toth—Defendants challenged Dr. Budoff's trial testimony regarding the amount of money Dr. Budoff personally received from Amarin. Trial Tr. 1940:2–13 (Toth Cross). At the same time, Defendants offered into evidence records from CMS Open Payments. Trial Tr. 1933:14–17 (Toth Cross). Importantly, Defense counsel never presented these records to Dr. Budoff. Trial Tr. 1942:5–8 (Toth Cross) (the Court expressed "concern[] that this information was not introduced during [Dr. Budoff's] examination to allow him the opportunity to say -- to challenge the information."). Moreover, as Dr. Toth testified, these records are "notoriously

inaccurate"[11] Trial Tr. 1931:22 (Toth Cross). Nevertheless, Dr. Budoff testified that he does receive consulting payments for his work with Amarin and other pharmaceutical companies. Trial Tr. 528:22–531:3 (Budoff Cross).

237. **Edward A. Fisher, M.D. (Defendants' Expert).** Dr. Fisher is a Professor of Cardiovascular Medicine, and Professor in the Departments of Medicine, Pediatrics and Cell Biology at the N.Y.U. School of Medicine. Dr. Fisher testified on behalf of Defendants on issues related to objective indicia of nonobviousness. Trial Tr. 922:1–1102:25 (Fisher Direct) (complete direct examination of Dr. Fisher).

238. Dr. Fisher was admitted as an expert in preventive cardiology and the investigation and treatment of lipid disorders and atherosclerosis in diabetics and other patients. *See* Trial Tr. 943:24–944:4 (Fisher Direct). Dr. Fisher testified that the mechanism by which VASCEPA achieved its dramatic cardiovascular reduction in cardiovascular risk is still not known (Trial Tr. 1031:8–16), and also provided testimony relating to the objective indicia of non-obviousness relating to diabetic patients.

239. **Jay W. Heinecke, M.D. (Defendants' Expert).** Dr. Heinecke is a Professor of Medicine at the University of Washington School of Medicine at the UW Medical Center in Seattle, Washington. Dr. Heinecke testified on behalf of Defendants on issues related to obviousness.

[11] Since its inception, the Open Payments database has been "plagued by significant shortcomings that call into question the accuracy of information published." PX 1220 (AMA "Open Payments" Guide) at 1. Because it is too difficult for physicians to contest inaccurate payments, *see* PX 1221 (Cagnetta & Ladd) at 1, and there are inconsistencies in how companies classify and report payments, the Open Payments database is replete with errors. One audit of the data reported for 25 physicians found that 34% of the payments were in error. *Id.* Based on these results, the auditors warned that "records of millions of dollars of purported payments to large numbers of physicians would be wrong." *Id.* Later, those auditors reviewed hundreds of data submissions from dozens of companies, only to find "even higher error rates." *Id.* Not surprisingly, public reviewers—citing warnings on the Open Payments website—have urged caution when relying on this data, noting that "[r]esearch payment can be especially prone to misinterpretation given that an entire institutional research grant . . . can be attributed to one principal investigator physician who receives a salary." PX 1223 (Sullivan) at 3.

240. Dr. Heinecke testified in support of Defendants' contention that the asserted patents would have been obvious. *See* Trial Tr. 710:3–916:16 (Heinecke Direct) (complete direct examination of Dr. Heinecke). Dr. Heinecke was admitted as an expert in the fields of lipoprotein metabolism and lipid disorders, *see* Trial Tr. 714:1–10 (Heinecke Direct), however he is not an expert in cardiology; has not treated patients since 2008; and does not recall treating a patient with severe hypertriglyceridemia since 2004. *See* Trial Tr. 832:21–833:17, 835:20–836:21 (Heinecke Cross). Moreover, Dr. Heneicke has no recollection of prescribing any of the omega-3 fatty acid products—including VASCEPA and Lovaza—that are currently approved by FDA for lowering TGs in patients with severe hypertriglyceridemia. *See* Trial Tr. 834:8–835:15 (Heinecke Cross).

241. **Ivan T. Hofmann (Defendants' Expert).** Mr. Hofmann is a Vice President and Managing Director at Gleason & Associates, P.C. Mr. Hofmann testified on behalf of Defendants on issues related to commercial success objective indicia of nonobviousness.

242. Mr. Hofmann was admitted as an expert in pharmaceutical economics. *See* Trial Tr. 1221:13–17 (Hofmann Direct). Mr. Hofmann testified about issues relating to whether VASCEPA is a commercial success. *See* Trial Tr. 1218:8–1311:7 (Hofmann Direct) (complete direct examination of Ivan Hofmann).

243. **Steven Ketchum, Ph.D. (Plaintiffs' Witness).** Dr. Ketchum is the President of Research & Development, a Senior Vice President, and the Chief Scientific Officer at Amarin Pharma, Inc. Trial Tr. 49:18–19 (Ketchum Direct).

244. Dr. Ketchum has a Ph.D. in Pharmacology from University College London. Trial Tr. 56:23–25 (Ketchum Direct). Dr. Ketchum has over 20 years of experience in late-stage drug development and clinical regulatory strategy, having led the filings of successful NDAs and sNDAs while serving in regulatory affairs and research & development roles at several pharmaceutical companies. Trial Tr. 57:10–62:20 (Ketchum Direct).

245. As head of Research & Development at Amarin, Dr. Ketchum oversees the scientific disciplines that flow into the drug development and registration process, including Amarin's clinical, pharmaceutical development, quality assurance, and regulatory affairs teams.

Trial Tr. 49:21–25 (Ketchum Direct). Since joining Amarin in February 2012, Dr. Ketchum has been involved in all facets of the VASCEPA clinical and regulatory program, from negotiating VASCEPA's first FDA approval in July 2012 to its newest FDA-approved indication in December 2019. Trial Tr. 50:11–51:6 (Ketchum Direct).

246. At trial, Dr. Ketchum introduced both Amarin and its sole commercial product, VASCEPA. Dr. Ketchum explained that Amarin is a small, "science-driven" company that has devoted over a decade and more than $500 million to the development of VASCEPA. Trial Tr. 50:3–10, 51:7–56:19 (Ketchum Direct). Dr. Ketchum explained that Amarin developed VASCEPA to address two unmet medical needs. Trial Tr. 52:11–54:1 (Ketchum Direct). First, Amarin sought to address the limitations of existing triglyceride-lowering medications approved for treatment of severe hypertriglyceridemia—e.g., LOVAZA, fenofibrates, and niacin—by developing a product that could robustly lower triglycerides in patients with severe hypertriglyceridemia (a) without raising bad cholesterol and (b) while having a favorable safety and tolerability profile. Trial Tr. 52:14–53:2 (Ketchum Direct). Second, Amarin sought to prove that VASCEPA could safely and effectively reduce the residual risk of major adverse cardiovascular events in patients who have elevated triglycerides, and who remain at high cardiovascular risk, despite statin therapy. Trial Tr. 53:3–54:1 (Ketchum Direct).

247. Dr. Ketchum then explained that, after successful clinical trials, Amarin won FDA approval to fill both medical needs: In July 2012, FDA approved VASCEPA as an adjunct to diet to reduce triglycerides in adult patients with severe hypertriglyceridemia. Trial Tr. 51:20–52:3, 65:11–20 (Ketchum Direct). More recently, in December 2019, FDA approved VASCEPA for a second indication, as an adjunct to maximally tolerated statin therapy to reduce the risk of major adverse cardiovascular events in patients who have elevated triglycerides and either have, or are at high risk for, cardiovascular disease. Trial Tr. 52:4–10, 65:21–22 (Ketchum Direct).

248. During the remainder of his direct examination, Dr. Ketchum described the years-long clinical development program that led to VASCEPA's two FDA-approved indications. Dr. Ketchum recounted how Amarin worked with FDA from spring 2008 through 2009 to obtain the

agency's consent to a three-prong clinical development program. Tr. 73:22–78:24 (Ketchum Direct). Dr. Ketchum then walked through each of Amarin's Phase 3 clinical trials: MARINE, ANCHOR, and REDUCE-IT. *See generally* Trial Tr. 78:25–117:7, 123:21–137:3, 150:10–161:22 (Ketchum Direct).

249. **Sean Nicholson, Ph.D. (Plaintiffs' Expert).** Dr. Nicholson was admitted as an expert in the economics of the pharmaceutical industry. Trial Tr. 1421:6–11 (Nicholson Direct). He testified about commercial success of VASCEPA and its nexus to the Asserted Claims. Trial Tr. 1417:13–1538:6 (Nicholson Direct) (complete direct exam of Nicholson).

250. Dr. Nicholson is a Professor in the Department of Policy Analysis and Management, the Director of the Sloan Program in Health Administration at Cornell University, and a Research Associate at the National Bureau of Economic Research. PX 1098 (Nicholson CV) at 2; Trial Tr. 1418:3–20 (Nicholson Direct). Prior to joining Cornell, he served as an Assistant Professor in Healthcare Systems at the Wharton School of the University of Pennsylvania. PX 1098 (Nicholson CV) at 2. He has a Ph.D. in Economics from the University of Wisconsin-Madison and an A.B. in Economics from Dartmouth College. Trial Tr. 1418:21–1419:2 (Nicholson Direct). His research and teaching specialty is the economics of healthcare, with a focus on the biotechnology and pharmaceutical industries. Trial Tr. 1419:3–7 (Nicholson Direct).

251. In his academic career, Dr. Nicholson has researched the economics of the healthcare industry, with an emphasis on the pharmaceutical competition, pricing, and innovation. Trial Tr. 1419:8–1420:7 (Nicholson Direct). In this field of study, he has published articles in leading academic journals and presented his research at academic conferences. *See* PX 1098 (Nicholson CV) at 2–7, 9–12; *see also* Trial Tr. 1420:8–12 (Nicholson Direct). He co-edited *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, published in 2012. Trial Tr. 1420:8–14 (Nicholson Direct).

252. In addition, he has served as a principal investigator on research projects sponsored by the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, the Robert Wood Johnson Foundation, and by leading biopharmaceutical companies.

Trial Tr. 1419:22–1420:1 (Nicholson Direct). He has also consulted and provided executive education to several biopharmaceutical companies. *See* PX 1098 (Nicholson CV) at 12–13.

253. Dr. Nicholson's research projects have included identifying what types of firms are most effective at developing drugs, assessing risk in the healthcare industry, and determining the value of new medical technologies. Trial Tr. 1419:14–21 (Nicholson Direct). He has done extensive research on the risks and uncertainties facing pharmaceutical companies. *See* PX 1098 (Nicholson CV) at 2–7.

254. **Carl Peck M.D. (Plaintiffs' Expert).** Dr. Peck was offered as an expert in FDA regulation of new and generic drugs including prescription drug labeling. Trial Tr. 1323:16–23 (Peck Direct)[12].

255. Dr. Peck is a physician scientist with five decades of combined experience in internal medicine, clinical pharmacology, clinical trial design and analysis, and the development and regulation of pharmaceutical products. Dr. Peck is board certified in internal medicine and clinical pharmacology, and he held several medical, research, and teaching posts over a twenty-year career in the U.S. Army Medical Corps. Trial Tr. 1315:2–1320:9 (Peck Direct).

256. Dr. Peck has significant FDA experience. From 1987 to 1993, Dr. Peck served as the Director of the Center for Drug Evaluation and Research (CDER), the FDA center responsible for evaluating and approving all new and generic drugs for use in humans. As the Director of CDER, Dr. Peck's responsibilities included reviewing and commenting on the sufficiency of studies supporting NDAs, ANDAs, and INDs, supervising other FDA scientists in their review of such studies, as well as reviewing, editing, and establishing standards for the format and content of prescription drug labels. Trial Tr. 1320:13–1322:7 (Peck Direct).

[12] In granting Dr. Peck's expert certification, the Court stated, "The request is granted. The Court will certify Dr. Peck as FDA -- as an expert in FDA regulations of new and generic drugs including *new* drug labels" rather than "prescription" drug labels. Trial Tr. 1323:20–23 (Peck Direct) (emphasis added). In any event, the discrepancy does not appear to affect the scope of Dr. Peck's expert certification.

257. Since leaving government service, Dr. Peck has directed the Center for Drug Development Science at Georgetown University and the University of California, San Francisco, and continued researching and teaching in the fields of drug development and regulation. As Founder and Chairman of NDA Partners, LLC, Dr. Peck also routinely consults with clients on clinical trial design and analysis and FDA's regulatory requirements for new drugs. Trial Tr. 1312:14–1313:4, 1318:18–1320:9 (Peck Direct).

258. **Jonathan I. Sheinberg, M.D. (Defendants' Expert).** Dr. Sheinberg was admitted as an expert in cardiology. Trial Tr. 562:25–563:14 (Sheinberg Direct).

259. Dr. Sheinberg is a board-certified cardiologist and is a senior staff cardiologist at the Baylor Scott & White Health Medical Center in Austin, Texas. Dr. Sheinberg is an invasive cardiologist with an interest in preventive cardiology and his practice consists of general cardiology, which covers all specialties within cardiology broadly. Trial Tr. 557:24–558:25 (Sheinberg Direct).

260. Dr. Sheinberg currently holds the title of Assistant Professor of Medicine at the University of Texas Medical Branch in Galveston. Dr. Sheinberg has not published any research in the field of cardiology or otherwise. Trial Tr. 561:16–562:18 (Sheinberg Direct).

261. **Peter Toth, M.D., Ph.D. (Plaintiffs' Expert)** Dr. Toth was admitted as an expert in lipidology, the treatment of severe hypertriglyceridemia, including severe hypertriglyceridemia, and the prevention and treatment of cardiovascular disease. *See* Trial Tr. 1560:11–17 (Toth Direct). Dr. Toth testified regarding the non-obviousness of the Asserted Patents, and about the clinical attributes of VASCEPA and the longstanding problems that it solved in the treatment of severe hypertriglyceridemia. *See* Trial Tr. 1546:9–1783:13 (Toth Direct) (complete direct examination of Dr. Toth).

262. Dr. Toth is the Director of Preventive Cardiology at the CGH Medical Center in Sterling, Illinois, where he makes recommendations based on developments in the field of cardiovascular disease prevention that guides the practice of other practicing physicians in the hospital. *See* PX 1172 (Toth CV) at 1–3; *see also* Trial Tr. 1547:7–18 (Toth Direct). He maintains

an active clinical practice where he treats over 400 patients per month, many of whom have elevated triglycerides and are at increased risk for cardiovascular events. PX 1172 (Toth CV) at 1-3; *see also* Trial Tr. 1547:19–1549:1 (Toth Direct). Dr. Toth has treated hundreds of patients with severe hypertriglyceridemia spanning the course of 24 years, since he began practicing medicine. Trial Tr. 1547:25-1549:1 (Toth Direct).

263. Dr. Toth also holds positions on the faculty at medical schools, including University of Illinois School of Medicine, Michigan State University College of Osteopathic Medicine, and Johns Hopkins School of Medicine. Trial Tr. 1549:25-1550:19 (Toth Direct). In his faculty positions, Dr. Toth instructs and supervises current medical students during their clinical rotations, lectures at Continuing Medical Education symposia, and collaborates on research concerning cardiovascular medicines. Trial Tr. 1551:23–1553:9 (Toth Direct).

264. Dr. Toth also holds leadership positions in various professional organizations, including as President-elect of the American Society of Preventive Cardiology, past-President of the National Lipid Association, past-President of the Midwest Lipid Association, and past-President of the American Board of Clinical Lipidology. Trial Tr. 1551:23-1553:9 (Toth Direct). As the President of the American Board of Clinical Lipidology, Dr. Toth oversaw the board certification process for physicians in the field of clinical lipidology. PX 1172 at 1–7, *see also* Trial Tr. 1551:23–1553:9 (Toth Direct).

265. Dr. Toth also performs and supervises clinical studies as a primary investigator and performs analytical research into data from clinical trials. *See* PX 1172 at 7–8. In total, he has served as a primary investigator for nine clinical trials involving the management of dyslipidemia, hypertension, diabetes, and cardiovascular risk factors. Trial Tr. 1554:20–1556:16 (Toth Direct).

266. Dr. Toth has authored or co-authored over 700 publications, including 375 research papers, 75 book chapters, and over 275 abstracts, the vast majority of which concern the fields of lipidology and cardiovascular disease prevention. *See* PX 1172 at 11–91; *see also* Trial Tr. 1557:15–1558:19 (Toth Direct).In addition to his research, Dr. Toth also consults for various pharmaceutical companies, including Amgen, Merck, Regeneron, and Amarin. Trial Tr. 1558:20–

1559:20 (Toth Direct). He performs this consulting work because it is "extremely important to advance medical science" and because "love[s] teaching [his] peers" about important products that can improve medical care. Trial Tr. 1559:15–20 (Toth Direct); Trial Tr. 1892:1–3 (Toth Cross). Dr. Toth testified that he has received some payments from Amarin in this connection, but that the estimates Defendants alleged—roughly $140,000 over a 6-year period—were inflated (Trial Tr. 1931:10–25 (Toth Cross)), and that the records on which Defendants relied in providing an estimate are "notoriously inaccurate." Trial Tr. 1931:22 (Toth Cross); *see supra* ¶ 236 n.10. In any event, the payment amount alleged by Defendants over a six-year period is amounts to an average of $23,000 a year before tax, and there is no indication that it affected Dr. Toth's candor in any way.

B. Deposition Testimony

267. **Jerald Andry, Pharm.D. (Defendant Hikma's Witness).** Jerald Andry is the Senior Director of Drug Regulatory Affairs and Medical Affairs at Hikma Pharmaceuticals USA Inc. Andry Dep. 8:15–23, 29:3–9 (Nov. 8, 2018).

268. **Jaya Ayyagari (Defendant DRL's Witness).** Jaya Ayyagari is the Director of Regulatory Affairs at Dr. Reddy's Laboratories, Inc. Ayyagari Dep. 5:9–21, 27:25–28:5 (Oct. 25, 2018).

269. **Harold E. Bays, M.D. (Third-Party Witness).** Dr. Bays is the Medical Director and President of Louisville Metabolic and Atherosclerosis Research Center. Dr. Bays received his medical degree and completed his internship, residency, and fellowship in endocrinology and metabolism at the University of Louisville School of Medicine. Over the course of his career, Dr. Bays has been an investigator in hundreds of clinical trials for cholesterol and lipid disorders, obesity, diabetes mellitus, hypertension, osteoporosis, and other metabolic and hormonal disorders. Dr. Bays submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents.

270. **Andrea Cady, Ph.D. (Defendant Hikma's Witness).** Andrea Cady is the Senior Director of Product Development at Hikma Pharmaceuticals USA Inc. Cady Dep. 9:5–16.

271. **Philip Lavin, Ph.D. (Third-Party Witness).** Dr. Lavin has a Ph.D. in Applied Mathematics from Brown University. Dr. Lavin is self-employed through Lavin Consulting LLC as a biostatistics consultant. Dr. Lavin submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents.

272. **Mehar Manku, Ph.D. (Third-Party Witness).** Dr. Manku is one of the named inventors of the Asserted Patents. He received his Ph.D. from Newcastle University in 1975. Thereafter, Dr. Manku began a more than four-decade career researching and studying fatty acids in animal models and humans, with particular focus on the metabolism of ethyl-eicosapentaenoic acid in the body. During his career, Dr. Manku held senior research positions with a number of companies focused on the development of fatty acids as medicines. Beginning in 2007, Dr. Manku served as Amarin's Vice President of Research and Development. Throughout his career at Amarin, Dr. Manku played a central role in the development of VASCEPA. Manku Dep. 8:22–9:17, 10:5–12:11, 14:19–16:6, 31:10–32:12, 48:19–50:11.

273. **Peter R. Mathers (Defendants' Expert).** Mr. Mathers is a partner in the Washington, D.C. law firm of Kleinfeld, Kaplan and Becker LLP, where he practices food and drug law. Mr. Mathers was retained by Defendants to provide opinions regarding issues relating to patent infringement. Mathers Dep. 11:13–24.

274. **Michael Miller, M.D. (Plaintiffs' Claim Construction Declarant).** Dr. Miller is Professor of Cardiovascular Medicine, Epidemiology and Public Health at the University of Maryland School of Medicine. Dr. Miller has served as the Director of the Center for Preventive Cardiology at the University of Maryland Medical Center since 1991. Amarin asked Dr. Miller to offer his expert opinion during claim construction regarding how a person of ordinary skill in the art would understand certain terms in the Asserted Claims.

275. **Ian Osterloh, M.D. (Third-Party Witness).** Dr. Osterloh is one of the named inventors of the Asserted Patents. He graduated from medical school in 1982, and obtained membership into the Royal College of Physicians in 1985. In 1986, Dr. Osterloh began a more than two-decade career in clinical research and development at Pfizer in the United Kingdom. In

2007, Dr. Osterloh joined Amarin as a consultant on the severe hypertriglyceridemia clinical research and development program. Osterloh Dep. 8:22–9:18, 22:24–23:24, 49:1–3.

276. **Anuj Srivastava, Ph.D. (Defendant DRL's Witness).** At the time of his deposition, Anuj Srivastava was the Senior Director of Strategic Portfolio & Business Development at Dr. Reddy's Laboratories, Inc. Srivastava Dep. 6:5–8, 17:15–18:15 (Oct. 18, 2018) ("Srivastava Deposition").

277. **Howard S. Weintraub, M.D. (Third-Party Witness).** Dr. Weintraub is the Clinical Director of the Center for the Prevention of Cardiovascular Disease at New York University Medical Center. Dr. Weintraub's research focuses on cholesterol, blood sugar, and cardiovascular disease, and he is the author or co-author of more than 30 scientific and technical papers. As a practicing cardiologist, Dr. Weintraub treats thousands of patients for lipid disorders annually. Dr. Weintraub submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents. Weintraub Dep. 8:19–9:7, 10:2–16, 114:20–115:19, 185:9–11 (Sep. 14, 2018) ("Weintraub Deposition").

X. JURISDICTION AND VENUE

278. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a) because it arises under the Patent Laws of the United States, 35 U.S.C. § 100, et seq. Pretrial Order ¶ 24 (ECF No. 295).

279. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b). Pretrial Order ¶ 25 (ECF No. 295).

280. For purposes of this action only, no party contests personal jurisdiction or venue in this Court. Pretrial Order ¶¶ 25–26 (ECF No. 295).

XI. DEFENDANTS INDUCE INFRINGEMENT OF ALL TEN ASSERTED CLAIMS

281. Defendants seek FDA approval for the same indication as VASCEPA—as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia—and Defendants' proposed prescribing information instructs physicians to prescribe the drug in a 4 g daily dose for this very indication. Further, Defendants' labels include

prescribing directions identical to the portions of the Vascepa label that instruct physicians to prescribe the product indefinitely as treatment for a chronic condition, with the expectation of certain effects on other lipids (e.g., avoidance of LDL-C increases and reduction in apoB). Defendants' Labels, like the VASCEPA Label, further instruct that these treatment effects may be achieved without concomitant lipid altering therapy. These instructions will "inevitably lead some physicians to infringe," thereby establishing intent to induce infringement. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017).

282. The evidence presented by Defendants at trial does not come close to refuting Amarin's evidence that Defendants' labels will inevitably lead some physicians to infringe. Trial Tr. 655:13–656:2 (Sheinberg Cross) (agreeing that at least some physicians will be induced to administer VASCEPA® for more than 12 weeks). So in an attempt to avoid infringement, Defendants have advanced a number of arguments that are either legally irrelevant or would seek to have physicians review the Defendants' labels in a vacuum.

283. For example, the evidence at trial established clinicians would understand Defendants' labels to be instructing physicians to treat patients with chronic severe hypertriglyceridemia long term. *See, e.g.*, *infra* ¶¶ 301–03. Defendants attempt to avoid this reality by arguing that if some physicians would administer Vascepa for a short term course of treatment, then there can be no inducement. Not only is short term use of VASCEPA® contrary to medical practice, Trial Tr. 390:1–15 (Budoff Direct); Trial Tr. 590:20–21, 592:21–22 (Sheinberg Direct); Trial Tr. 672:11–19 (Sheinberg Cross), but it does not save Defendants from inducement. For example, another district court recently found induced infringement in a case involving strikingly similar facts, with a claim directed to treatment "for at least 12 months." *See Sanofi v. Glenmark Pharm. Inc., USA*, 204 F. Supp. 3d 665, 683–84 (D. Del. 2016), aff'd, 875 F.3d 636 (Fed. Cir. 2017). There, as here, the indicated use was (1) for a chronic disorder for which clinicians intended administration of the drug indefinitely, (2) the label did not limit the duration of the treatment, and (3) the label reported the length of the clinical trial. *Id*. The court found the length of the trial included on the label would encourage clinicians to administer for at least that claimed duration

and therefore found infringement of the duration claim limitation. *Id*. at 683–84. Given the parallel facts, this Court should reach the same result here.

284. Defendants also seek to avoid infringement of some of the Asserted Claims by arguing that their labels will not induce infringement of the lipid effect limitations or the without concomitant lipid altering therapy limitations. But it is undisputed that defendants labels, if approved, establish that Defendants' ANDA Products are safe and effective to reduce TGs without raising LDL-C, *see infra* ¶¶ 321–37, and to reduce apo B, *see infra* ¶¶ 338–42. Moreover, the proposed indication is for monotherapy. In other words, if Defendants' ANDA Products are approved, then they will be approved as safe and effective for use without concomitant lipid altering therapy. Thus, Defendants will induce infringement because the intent prong is established when "the label, taken in its entirety . . . recommend[s] or suggest[s] to a physician" that the drug used in the claimed method of treatment is safe and effective for causing the effects described in the patent claims. *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1324 (Fed. Cir. 2012).

285. As explained more fully below, the trial record establishes that Defendants should be found liable for induced infringement. *Vanda Pharm. v. West-Ward Pharm.*, 887 F.3d 1117, 1132 (Fed. Cir. 2018) ("Even if not every practitioner will prescribe an infringing dose, that the target dose range 'instructs users to perform the patented method' is sufficient to 'provide evidence of [West-Ward's] affirmative intent to induce infringement.'").

A. Infringement Legal Standard

286. A patent is infringed where the accused product meets all of the claim limitations, either literally or by equivalence. *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989). Determining infringement is a two-step process. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*). First, the court must construe the Asserted Claims, as a matter of law, to ascertain their meaning and scope. *Id.* Second, the trier of fact must compare the properly construed claims against the accused product. *Id.*

287. "Infringement is a question of fact." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010). Infringement need be proven only by a preponderance of the evidence.

SmithKline Diagnostics, Inc. v. Helena Labs. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988). All probative evidence, including circumstantial evidence, is considered when determining infringement. *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

288. Under 35 U.S.C. § 271(e)(2)(A), the filing of an ANDA pursuant to 21 U.S.C. § 355(j) seeking FDA approval to market a generic form of a drug claimed in a patent "constitutes a technical infringement for jurisdictional purposes." *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013). "But the ultimate infringement question" in a Hatch-Waxman case "is determined by traditional patent law principles." *Id.*

289. Because an ANDA applicant has not yet marketed its drug product, the court's infringement analysis involves a "hypothetical inquiry" that focuses "on the product that is likely to be sold following FDA approval." *Abbotts Labs. v. TorPharm., Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 2002). If the product that the ANDA applicant is asking FDA to approve falls within the scope of an issued patent claim, a judgment of infringement must necessarily ensue. *Abbotts Labs.*, 300 F.3d at 1373; *Sunovion Pharm.*, 731 F.3d at 1278.

290. Anyone who "actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Here, where Defendants have filed ANDAs seeking approval for their proposed generic products, "induced infringement turns on whether [the Defendants] have the specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products to treat [patients in accordance with the claimed methods]. In other words, . . . whether the label encourages, recommends, or promotes infringement." *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019) (internal citation omitted).

291. Determining what a product label "recommend[s] or suggest[s] to a physician" requires reading the product label from the viewpoint of the clinician. *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1324 (Fed. Cir. 2012); *see also Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Inc.*, 887 F.3d 1117, 1131 (Fed. Cir. 2018) (citing expert testimony that clinicians read "laboratory tests" in the product label as encouraging clinicians to perform the "genotyping

tests" described in the asserted patent claims). In addition, the inducement inquiry is not limited to particular sections of the drug labeling—the court must consider the labeling as a whole. *Bayer*, 676 F.3d at 1324; *See, e.g.*, *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 645–46 (Fed. Cir. 2017) (relying on the Clinical Studies section of the label); *Vanda*, 887 F.3d at 1131 (relying on the Dosage and Administration and Pharmacokinetics sections of the label). It is only when "the label, *taken in its entirety*, fails to recommend or suggest *to a physician* that [the drug] is safe and effective for inducing the claimed combination of effects in patients" is intent to induce infringement lacking. *Bayer* 676 F.3d at 1324 (emphasis added).

292. In their Rule 52(c) Motion for Judgment at trial, Defendants argued that, to find induced infringement, the indicated use in Defendants' proposed labeling must be "coextensive with or required the patented use." Trial Tr. 549:4–6. But even the case Defendants cite, *Grunenthal*, contains no such requirement. As quoted above, the court there reiterated the prevailing test that labeling induces infringement if it "encourages, recommends, or promotes infringement." 919 F.3d at 1339. Indeed, the Federal Circuit has repeatedly made clear that proposed generic labeling induces infringement if it "encourages, recommends, promotes, or suggests" an infringing use. *See, e.g.*, *Vanda*, 887 F.3d at 1129; *Bayer*, 676 F.3d at 1324; *Sanofi*, 875 F.3d at 644; *see also Takeda Pharm. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) (active inducement shown when the label "[s]uggests that an infringing use 'should' be performed"). The law does not demand that patent holders show that the use induced by the proposed labeling must be "coextensive with" the patented use or that the labeling "require" the patented use.

293. To the contrary, the law is clear that a patent holder need not show that *all* physicians will use the generic drug in an infringing manner. Rather, "evidence that the product labeling that Defendants' seek would inevitably lead *some physicians* to infringe establishes the requisite intent for inducement." *Eli Lilly & Co. v. Teva Parenteral Meds.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017) (emphasis added); *see also Vanda*, 887 F.3d at 1132 ("Even if not every practitioner will prescribe an infringing dose, that the target dose range 'instructs users to perform

the patented method' is sufficient to 'provide evidence of [West-Ward's] affirmative intent to induce infringement.").

294. In their pretrial brief, Defendants asserted that the existence of a substantial noninfringing use for a proposed product precludes a finding of induced infringement. The Federal Circuit has expressly rejected this argument, stating that "there is no legal or logical basis for the suggested limitation on inducement." *Sanofi*, 875 F.3d at 646; *see also Vanda*, 887 F.3d at 1133 ("[E]ven if the proposed ANDA product has substantial noninfringing uses, West-Ward may still be held liable for induced infringement."); *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1364 (Fed. Cir. 2012) ("The existence of a substantial non-infringing use does not preclude a finding of inducement.").

295. In *Sanofi*, for example, the Federal Circuit observed that 77% of the prescriptions were for an infringing use, leaving 23% of the prescriptions directed to noninfringing uses. 875 F.3d at 645. Even in the face of these noninfringing uses, the Federal Circuit found that "the content of the label in this case permits the inference of specific intent to encourage the infringing use." *Sanofi*, 875 F.3d at 646. The court distinguished *Sanofi* from a case where a defendant's product instructions "encouraged a noninfringing use in a way that showed an intent to discourage infringement." *Sanofi*, 875 F.3d at 646.

B. Defendants' Labels Will Induce Clinicians to Administer Defendants' ANDA Products to Severely Hypertriglyceridemic Patients for at Least 12 Weeks

296. All of the Asserted Claims require the administration of the claimed pharmaceutical composition for at least about 12 weeks. PX 21 ('728 Patent) at Claims 1, 16 ("for a period of 12 weeks"); PX 30 ('560 Patent) at Claims 4, 17 ("for a period of 12 weeks"); PX 22 ('715 Patent) at Claim 14, ("for a period of at least 12 weeks"); PX 25 ('677 Patent) at Claims 1, 8 ("period of at least about 12 weeks"); PX 31 ('929 Patent) at Claims 1, 5 ("for at least about 12 weeks"); PX 26 ('652 Patent) at Claim 1 ("for a period of about 12 weeks"); *see also* Trial Tr. 391:25–392:9 (Budoff Direct). Although the precise language used in each Asserted Claim varies slightly, the same analysis applies for each claim. Trial Tr. 392:10–14 (Budoff Direct).

297. The relevant inquiry is whether defendants' proposed labeling[13] taken in its entirety will "inevitably lead some physicians" to be encouraged to administer defendants' generic products to patients with severe hypertriglyceridemia for at least 12 weeks. *Eli Lilly*, 845 F.3d at 1369. The evidence here is overwhelming that the proposed labeling as a whole will encourage clinicians to prescribe EPA for at least 12 weeks. *Vanda*, 887 F.3d at 1132 ("Even if not every practitioner will prescribe an infringing dose, that the target dose range 'instructs users to perform the patented method' is sufficient to 'provide evidence of [West-Ward's] affirmative intent to induce infringement."). Defendants' argument to the contrary ultimately relies on the assertion that, as long as it might be possible to use the drug in a non-infringing manner consistent with the labeling, there cannot be inducement. As explained above, that is not the law.

1. Defendants' Proposed Labels Encourage Long-Term Use

298. ***Indications and Usage Section***. Defendants proposed generic products are "indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." Joint Stipulations of Fact ¶¶ 200, 212, 224 (ECF No. 324). As Dr. Budoff explained, a physician understands this indication to be directed to reducing TGs *and* maintaining that reduction. Trial Tr. 364:19–365:18, 367:11–368:20 (Budoff Direct); Trial Tr. 536:22–537:15 (Budoff Re-Direct).

299. This understanding is consistent with medical practice, in which a clinician's goal is "to get the triglycerides below and maintain them below 500" in order to avoid the risk of pancreatitis. Trial Tr. 331:18–20 (Budoff Direct); Trial Tr. 673:22–674:4 (Sheinberg Cross) (agreeing that "in medical practice the goal for triglyceride reduction . . . in patients with severe hypertriglyceridemia is to both reduce triglycerides and maintain that reduction"). Indeed, Dr. Fisher, one of Defendants' experts, agreed that "the indication is to reduce below 500 and to maintain that reduction below 500." Trial Tr. 1209:21–1210:8 (Fisher Cross); *see also* Fisher Dep.

[13] Because Defendants' proposed labels are materially identical to the VASCEPA label, opinions expressed about the statements in the VASCEPA label related to infringement apply equally to Defendants' labels and vice versa. Trial Tr. 363:3–10 (Budoff Direct); Trial Tr. 601:14–18 (Sheinberg Direct); Trial Tr. 649:5–11 (Sheinberg Cross).

72:3–8 ("Q: . . . You refer to the indication of Vascepa as keeping triglycerides below 500 milligrams per deciliter in a severely hypertriglyceridemic patient, correct? A: Yes.").

300. Not only do both parties' experts agree that the indication for treating patients with severe hypertriglyceridemia is to reduce and *maintain* that reduction, but it is clear from FDA's medical review of VASCEPA—a document that Defendants contend informs prescribers' understanding of Defendants' labeling[14]—that FDA approved VASCEPA for the reduction of TGs in patients with severe hypertriglyceridemia *and the maintenance of that reduction*. PX 289 (VASCEPA FDA Medical Review) at 67.

301. Prescribers also understand that severe hypertriglyceridemia is generally associated with an underlying genetic disorder. PX 289 (VASCEPA FDA Medical Review) at 40 ("Patients with very high TG have a strong genetic component to their disease"); Trial Tr. 383:10–385:10 (Budoff Direct) (discussion of this portion of PX 289 FDA Medical Review); Trial Tr. 671:2–6 (Sheinberg Cross) (agreeing that "the Medical Review reflects important background information that a person of ordinary skill in the art would understand and bring to bear when using Defendants' ANDA products as indicated"). The FDA Medical Review of VASCEPA also confirms that because severe hypertriglyceridemia has a strong genetic component, long-term therapy is required. PX 289 (VASCEPA FDA Medical Review) at 142 (FDA identifying VASCEPA as a "chronically administered drug" by checking the "yes" box for a content parameter only applicable to chronically administered drugs); Trial Tr. 105:11–108:14 (Ketchum Direct) (discussion of FDA Medical Review's identification of VASCEPA as "chronically administered drug").

302. In addition to the FDA Medical Review of VASCEPA, numerous documents in the trial record also confirm that severe hypertriglyceridemia has a strong genetic component, requiring long-term therapy. PX 269 (Miller 2011) at 12, Tbl. 5 (listing "Genetic" as the first cause

[14] *See* Trial Tr. 671:2–6 (Sheinberg Cross) (confirming his view that the medical review "reflects important background information that a person of ordinary skill in the art would understand and bring to bear when using defendants' ANDA products as indicated"); Mathers Dep. 90:24–91:4 (Medical Review is "relevant to [] the assessment of what the approval means and what was intended").

of severe hypertriglyceridemia); PX 288 (Karalis) at 10; Trial Tr. 374:2–380:16 (Budoff Direct) (discussion of PX 288 Karalis Review); PX 277 (Jacobson) at 154; Trial Tr. 386:4–388:3 (Budoff Direct) (discussion of PX 277 NLA Guidelines); *see supra* ¶ 22.

303. As a result, prescribers perceive severe hypertriglyceridemia as generally a chronic condition requiring long-term drug therapy. *See supra* ¶¶ 22–24; Trial Tr. 367:23–25 (Budoff Direct) ("[C]linicians in the field will know that severe hypertriglyceridemia is largely a genetic problem, a lifelong problem, and requires lifelong therapy."); Trial Tr. 373:12–389:25 (Budoff Direct) (discussing background knowledge clinicians bring to bear when reading the VASCEPA label, relating to the chronic nature of severe hypertriglyceridemia). "[T]he average clinician practicing in the field will prescribe VASCEPA for long-term therapy which will encompass a period of 12 weeks." Trial Tr. 367:5–7 (Budoff Direct). Dr. Sheinberg agreed that "sometimes severe hypertriglyceridemia is a chronic condition that requires indefinite drug treatment," even if his estimate of the percentage of chronic cases is lower than that of the other witnesses. Trial Tr. 696:16–19 (Sheinberg Cross).

304. Similarly, physicians understand that, for severely hypertriglyceridemic patients, maintaining the TG reduction achieved by TG-lowering medication requires the medication to be administered for the long term, to avoid the substantial risk that a patient's TG levels will rise when medication is discontinued. *See* Trial Tr. 536:22–537:5 (Budoff Re-Direct) ("[O]nce a severely hypertriglyceridemic patient's triglyceride levels have been reduced" therapy is not complete because "if you stop the therapy, in most cases it will go back up . . . in the vast majority of patients triglycerides will not stay below 500 without additional medical therapy"); Trial Tr. 378:21–379:2 (Budoff Direct) ("If [a patient's] triglyceride levels are still in the high range, then I know if I stop Vascepa their triglycerides will go back up to baseline."); Trial Tr. 1174:22–1175:1 (Fisher Cross) ("[F]requently a patient is kept on triglyceride lowering, essentially, as a prophylactic to make sure that the triglycerides are maintained below 500"); *see also* Trial Tr. 682:8–12 (Sheinberg Cross) (agreeing that monitoring for increases in TG levels is consistent with his practice). As Dr. Fisher conceded on cross-examination, even for motivated patients, it takes 6

months for lifestyle changes to effect a reduction in body mass sufficient for them to stop their medication. Trial Tr. 1175:2–7 (Fisher Cross); *see also* PX 288 (Karalis) at 10 (cautioning that if TG-lowering medication is withdrawn, the TG levels will need to be monitored closely for any rise in the TG levels").

305. That physicians will be encouraged to prescribe EPA for at least 12 weeks is confirmed by real-world evidence. Both Drs. Budoff and Sheinberg testified that their typical practice for writing prescriptions is to prescribe either a one-month supply with three refills (for a four-month supply) or a three-month prescription with three refills (for a twelve-month supply). Trial Tr. 391:2–8, 393:10–21 (Budoff Direct); Trial Tr. 663:2–19 (Sheinberg Cross). At the time physicians write the prescription, their intent is for the patient to take EPA for the prescribed time. Trial Tr. 391:9–12 (Budoff Direct)

306. ***Dosage and Administration***. As explained further below, the Dosage and Administration section of Defendants' proposed labeling further encourages long-term administration by instructing prescribers to address transient causes before administering the drug.

307. Specifically, the Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA's labeling, consists of two sub-sections and directs prescribers to take certain steps ***before*** administering VASCEPA, as the very title of Subsection 2.1, "Prior to Initiation of VASCEPA," makes clear. Trial Tr. 368:21–369:8 (Budoff Direct) ("So prior to starting or prescribing Vascepa, [the label] give[s] you some steps that you should take and accomplish prior to implementing treatment."). The causes identified in this section of the labels include other diseases or conditions, medications, and inappropriate nutritional intake and physical activity, otherwise referred to as "short term," "secondary," "reversible," or "transient" causes of severe hypertriglyceridemia. Trial Tr. 369:9–19, 370:9–17 (Budoff Direct); *see also supra* ¶¶ 22–25. By encouraging physicians to try other approaches to address patients with transient causes of severe hypertriglyceridemia, the labeling directs prescribers to use VASCEPA (or one of Defendants' ANDA Products) in those patients whose very high triglycerides are not readily addressed through lifestyle counseling or other means—that is, in patients whose severe

hypertriglyceridemia is chronic or otherwise requires long-term treatment. Trial Tr. 370:23–371:10 (Budoff Direct).

308. To be sure, physicians retain the discretion to prescribe VASCEPA for all their severely hypertriglyceridemic patients, without trying lifestyle counseling first, and indeed may choose to do so where the risk of pancreatitis is judged sufficiently imminent. However, that is not the use encouraged by the drug labeling, which instructs physicians to address transient causes first and encourages use of the drug in chronic cases resistant to lifestyle changes. Trial Tr. 1377:12–1378:15 (Peck Cross). Indeed, both sides' experts agreed that administering VASCEPA without first trying diet and exercise would be an off-label use. *See* Trial Tr. 370:16–17 (Budoff Direct) ("It would be an off-label use to use Vascepa before implementing diet and exercise."); Trial Tr. 1207:16–24 (Fisher Re-Cross) ("technically" off-label).

309. ***Clinical Studies Section***. There is no dispute that "an understanding of the clinical trials for a medication is vital to using that medication," Trial Tr. 665:10–13 (Sheinberg Cross), and the parties also agree that "one of the goals" of the Clinical Studies section in a drug label "is to facilitate a prescriber's understanding of how to use the drug safely and effectively." Mathers Dep. 170:3–7; *see also* Trial Tr. 665:14–666:7 (Sheinberg Cross) (agreeing with Mr. Mathers). Thus, prescribers use the Clinical Studies section of the labeling to understand how to prescribe a drug to their patients.

310. The Clinical Studies section of Defendants' labels, like VASCEPA's label, reports the results of the clinical study that established the effectiveness of EPA 4 g per day in treating patients with severe hypertriglyceridemia. In describing the important details of the study, this section of the labeling expressly states that patients were administered icosapent ethyl 4 g per day "for 12 weeks." PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9. As Defendants' regulatory expert Mr. Mathers conceded, Defendants' proposed labeling reports the treatment effects only at 12 weeks, not earlier, and thus reflects approval for reducing TGs below 500 mg/dL and maintaining that reduction through 12 weeks:

> Q. So defendants' proposed labeling shows only the treatment effects that persist at 12 weeks and not the effects achieved at four weeks, correct?
>
> A. The only clinical data provided is the data at 12 weeks—are the data at 12 weeks.
>
> Q. And nothing in defendants' proposed labeling limits the approval they're seeking to simply achieving TG reduction below 500 mg/dL without maintaining that reduction through 12 weeks, correct?
>
> A. The approval wasn't limited to—to—the—that's not the approved indication or the basis for it.

Mathers Dep. 97:2–16.

311. The Clinical Studies section contains only the effects on the patients' TGs and other lipid levels after 12 weeks of administration; no data for other time frames is available to clinicians in the labels. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; *see also* Trial Tr. 666:9–667:6 (Sheinberg Cross); Mathers Dep. 96:19–97:16. This is meaningful to clinicians because they "try to follow the prescribing information, and if the prescribing information was done at 12 weeks, then that informs the physician, that instructs the physician that you should wait 12 weeks to reassess lipids to see what the full effect of your treatment is, because [clinicians'] goal when putting [patients] on Vascepa is to achieve the results in Table 2." Trial Tr. 372:3–12 (Budoff Direct). The labels therefore encourage, recommend, promote, or suggest that clinicians should administer Defendants' ANDA Products for at least 12 weeks to achieve the drug effects reported in the labeling. *See* Trial Tr. 372:16–374:5 (Budoff Direct) ("[T]he only way I can compare my patient to the label and what's being encouraged is to follow the instructions that are given, and the instructions here are to treat for 12 weeks.").

312. In remarkably similar circumstances, a recent district court opinion found infringement with respect to a claim directed to treatment "for at least 12 months." *Sanofi*, 204 F. Supp. 3d at 683–84. There, as here, the Indications and Usage section of the labels did not limit the duration of the treatment. *Id.* at 683. There, as here, expert testimony established that the indicated use was for

a "chronic disorder" for which clinicians intended administration of the drug "indefinitely." *Id.* There, as here, the label reported a clinical trial and the length of that trial would further encourage clinicians to administer for at least the claimed duration of 12 months. *Id.* at 683–84. The same result should be reached here with respect to the "12 weeks" limitations.

313. The Clinical Studies section of Defendants' labeling, if approved, will thus instruct clinicians to administer Defendants' ANDA Products for at least 12 weeks to obtain the treatment effect described in the labeling. Trial Tr. 371:20–373:11 (Budoff Direct). As a result of that instruction, physicians will administer Defendants' ANDA Products for at least 12 weeks.

2. FDA Approved VASCEPA for, and Accordingly Would Approve Defendants' ANDA Products for, Long-Term Use

314. Defendants' labels are not "silent" as to duration of therapy. Trial Tr. 1334:23–1335:3 (Peck); *see also* Mathers Dep. 104:10–21. As Dr. Peck, Amarin's expert in FDA regulation of new and generic drugs including prescription drug labeling testified, at least three sections (*i.e.*, the Indications and Usage, Dosage and Administration, and Clinical Studies sections) speak to duration of treatment, Trial Tr. 1335:4–9 (Peck Direct), and encourage administration of EPA for at least 12 weeks. In addition, Mr. Mathers, Defendants' FDA regulatory expert who testified by deposition, largely confirmed Dr. Peck's testimony. *See, e.g.*, Mathers Dep. 104:10–21.

315. The indication in Defendants' proposed labeling is for long-term use. The Indications and Usage section of a drug label will include a "limitation of use" limiting the duration of treatment with a drug if there is a safety or efficacy reason to limit the duration of use (for example, because a drug is thought to be effective only for a period of time, or if continued use creates a safety issue). Trial Tr. 1335:21–1336:6 (Peck Direct); PX 573 (FDA Guidance Indications and Usage) at 13–16; *see also* Mathers Dep. 116:4-9. The Indications and Usage section of the VASCEPA label does not limit duration of use. Trial Tr. 1339:1–3 (Peck Direct); Trial Tr. 368:3-8 (Budoff Direct); PX 1186 (VASCEPA Label 2019) at 2; PX 1203 (Hikma 2019 Proposed Label) at 2; PX 1209 (DRL 2020 Proposed Label) at 2. This absence of a duration limitation reflects that FDA approved VASCEPA to reduce TGs and maintain that reduction over

the long-term. Trial Tr. 1338:8–1339:6 (Peck Direct); *see also* PX 289 (VASCEPA FDA Medical Review) at 142 (FDA reviewer specifically noted that VASCEPA met particular guidelines for "chronically administered drugs," while also indicating that requirements "[f]or drugs not chronically administered (intermittent or short course)" were not applicable to VASCEPA); Trial Tr. 105:11–108:14 (Ketchum Direct). FDA did not require a statement regarding duration in the Indications and Usage section because FDA considered severe hypertriglyceridemia to be a chronic condition that requires long-term therapy. Trial Tr. 1373:19–1374:1 (Peck Direct).

316. Similarly, if it is known that a drug provides no additional benefit past a certain duration of treatment, the Dosage and Administration section of the label should identify that duration. Trial Tr. 1342:15–1343:4 (Peck Direct); PX 572 (FDA Guidance: Dosage and Administration) at 7–8; *see also* Mathers Dep. 101:14–18. The Dosage and Administration section of the VASCEPA label does not limit the duration of use of VASCEPA. Trial Tr. 1344:15–17 (Peck Direct). The absence of a duration limitation in this section conveys that VASCEPA's benefit is not thought to cease after a particular duration of treatment, Trial Tr. 1343:5–9 (Peck Direct), which indicates that VASCEPA was approved for long-term use to reduce TGs and maintain that reduction. Trial Tr. 1344:3–14 (Peck Direct).

317. FDA guidance states that, when a drug is approved for a chronic condition and there are no concerns with long-term use, the length of the clinical trial should be described only in the Clinical Studies section. That is consistent with how the VASCEPA label is written. Trial Tr. 1339:7–1341:1 (Peck Direct); PX 573 (FDA Guidance: Indications and Usage) at 16. Taken together with the expectation that physicians will look to the Clinical Studies section for guidance on how long to use the drug when writing a prescription, Trial Tr. 1393:25–1394:16 (Peck Direct), the Clinical Studies section of Defendants' labeling encourages treatment for 12 weeks or more. Trial Tr. 1393:25–1394:19 (Peck Direct); *see also* Trial Tr. 371:25–372:19 (Budoff Direct); Mathers Dep. 83:6–10, 12–16.

318. Labeling for other drugs Dr. Sheinberg considered in his testimony are instructive. The Lovenox label demonstrates that when an indication is approved for a short-term duration, the

labeling states the duration. PX 285 (Lovenox Label) at 4–5; *see also* Trial Tr. 388:9–389:25 (Budoff Direct). But when drugs are approved for chronic indications, like statins are for reducing LDL-C, the product labels do not include a duration of use. DX 1986 (Lipitor Label 2019) at 3; *see* Trial Tr. 662:14–663:1 (Sheinberg Cross) (explaining that patients are on a statin indefinitely even after the patients' LDL-C levels drop below their goal level). There can be no question that physicians understand the absence of a duration of use in labeling as an indication that a drug should be prescribed long-term. Indeed, Dr. Sheinberg testified that he prescribes statins for long-term use. *Id.*

319. Analyzing Defendants' proposed labels (or the VASCEPA label) with the additional context of FDA's guidance and practice, further confirms that VASCEPA is—and Defendants' ANDA Products by extension will be—approved for chronic administration. The disclosures in the labels, which are driven by FDA labeling standards for chronically administered drugs, encourage clinicians to prescribe VASCEPA for at least 12 weeks.

C. Defendants' Labels Will Induce Clinicians to Administer Defendants' ANDA Products to Severely Hypertriglyceridemic Patients with the Intent to Reduce TGs without Raising LDL-C and to Reduce Apo B

320. Several limitations in the Asserted Claims require bringing about certain lipid effects. Specifically, there are limitations relating to avoiding a substantial increase in LDL-C, achieving reduction of certain levels of TGs, and achieving reduction in apo B. Defendants' proposed labeling will induce physicians to infringe each of these limitations.

1. "to effect a reduction in triglycerides without raising LDL-C"

321. As an initial matter, Defendants' experts have not contested that Defendants' labels will encourage clinicians to use Defendants' ANDA Products "to effect a reduction in triglycerides." Trial Tr. 656:17–22 (Sheinberg Cross); *see* Trial Tr. 848:5–7 (Heinecke Direct); Trial Tr. 1113:19–1114:3 (Fisher Direct). Defendants', however, apparently do dispute that their labels will encourage physicians to prescribe EPA to reduce TGs without raising LDL-C. For the reasons explained below, Defendants are incorrect.

322. With VASCEPA, Amarin was able to achieve something that had never been achieved before—development of a method of treatment with a drug for severe hypertriglyceridemia that reduces TGs without raising LDL-C. This unique and beneficial lipid profile is described in the VASCEPA labeling and, accordingly, Defendants' proposed labeling. Clinicians who read Defendants' labels as a whole will be encouraged to administer EPA to achieve these unique results: a reduction in TGs without raising LDL-C.

323. ***Indications and Usage Section.*** The Indications and Usage section of Defendants' labeling, like the same section in the VASCEPA labeling, states that Defendants' ANDA Products are "indicated . . . to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dl) hypertriglyceridemia." Joint Stipulations of Fact ¶¶ 200, 212, 224 (ECF No. 324). The plain language of this section encourages clinicians to administer VASCEPA to reduce TGs in severely hypertriglyceridemic patients. Trial Tr. 656:17–22 (Sheinberg Cross) ("Q. And so do you agree with me that this statement in the indications and usage section encourages doctors to administer Vascepa to patients to reduce triglyceride levels in subjects having fasting baseline triglyceride levels of 500 milligrams per deciliter or higher? A. As an adjunct to diet, yes.").

324. ***Dosage and Administration Section.*** The Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA's labeling, instructs clinicians to "[a]ssess lipid levels before initiating therapy." PX 1186 (VASCEPA Label 2019) at 2; PX 1203 (Hikma 2019 Proposed Label) at 2; PX 1209 (DRL 2020 Proposed Label) at 2. This instruction is then reinforced by the Patient Information section, which advises patients that "[y]our doctor may do blood tests to check your triglycerides and other lipid levels while you take VASCEPA." Mathers Dep. 134:4–9; *see* PX 1186 (VASCEPA Label 2019) at 13; PX 1203 (Hikma 2019 Proposed Label) at 9; PX 1209 (DRL 2020 Proposed Label) at 11. As Mr. Mathers explained, the Patient Information section of the labeling is informative to both prescribers and patients and serves to remind prescribers of the "standard of care to monitor" triglycerides and other lipids in patients who are receiving VASCEPA. Mathers Dep. 123:8–15; 132:20–133:13. This instruction in the labeling to monitor patient lipid levels is then further illuminated by the Clinical Studies

section, which is intended to "call out those parameters that are important to clinical decision-making" and which, here, identifies TGs, LDL-C, and apo B (among other) as clinically relevant. Mathers Dep. 134:10–15, 134:17–22; 135:5–8, 135:10–18; *see also id.* at 144:14–18, 144:20 (to be disclosed in the Clinical Studies section, clinical endpoints must be "well documented and statistically and clinically meaningful").

325. Thus, Defendants' proposed labeling advises clinicians that the patient's lipid panel—including the patient's TG and LDL-C levels—is an important consideration for clinicians when treating severe hypertriglyceridemia. Trial Tr. 404:5–18 (Budoff Direct); Mathers Dep. 134:10–22 (TGs, LDL-C, non-HDL-C, total cholesterol, HDL-C, VLDL-C, and apo B—identified in the Clinical Studies section as potentially "relevant parameters to measure on a routine basis and to monitor."). Indeed, it is standard practice for clinicians to obtain a standard lipid panel, including LDL-C measurements, when prescribing any cholesterol lowering medication. Trial Tr. 404:19–24 (Budoff Direct); *see* Trial Tr. 658:6–16 (Sheinberg Cross) (in Dr. Sheinberg's own practice, he uses an "advanced lipid panel" which also includes "additional biomarkers that are not in the standard lipid panel" such as apo B).

326. ***Clinical Studies Section.*** The Clinical Studies section of drug labeling is vital to understanding the effects of the drug. *See* Trial Tr. 665:1–13 (Sheinberg Cross). Among other things, it serves to "facilitate a prescriber's understanding of how to use the drug safely and effectively," and "call[s] out those parameters that are important to clinical decision making." Mathers Dep. 170:3–7; 135:5–8, 135:10–18. Here, not only does this section report that patients experienced a 5% reduction in LDL-C compared to baseline and a 2% reduction in LDL-C compared to placebo, the Clinical Studies section also states that "[t]he reduction in TG [triglycerides] observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; *see also* Trial Tr. 405:5–406:7 (Budoff Direct).

327. That the Clinical Studies section both reports the lack of increase in LDL-C in Table 2 and then expressly calls out the drug's ability to reduce TGs without raising LDL-C in the text below clearly highlights that information for prescribing clinicians and emphasizes (in Mr. Mathers words) FDA's judgment that the information is "important to clinical decision-making." Mathers Dep. 135:5–8, 135:10–18; s*ee also* Trial Tr. 406:2–6 (Budoff Direct) ("an emphasis to the clinician that this is an important finding"). Defendants' proposed labeling will inform prescribers that the drug is safe and effective for administration to patients with severe hypertriglyceridemia to reduce TGs without raising LDL-C. Further, the prominence of the information about LDL-C is a recognition by FDA that such information is particularly important for prescribers. "FDA specifically approved the statement in the [labeling] that the reduction in TG observed with Vascepa is not associated with elevations in LDL-C levels relative to placebo," Mathers Dep. 186:3–8; *see also* Mathers Dep. 146:2–9, 146:11–13 (FDA found this to be a truthful statement), and found that the statement is relevant to Vascepa's approved use, Mathers Dep. 188:5-12, 188:14–16.

328. Indeed, VASCEPA's ability to reduce TGs without raising LDL-C, as depicted in the Clinical Studies section, is a primary reason clinicians choose to prescribe VASCEPA over other available medications. Trial Tr. 406:7–407:6 (Budoff Direct).

329. ***Warnings and Precautions Section.*** The Warnings and Precautions section in Defendants' labeling, like the same section in VASCEPA's labeling, omits any warning that patients' LDL-C levels may rise as a result of treatment. PX 1186 (VASCEPA Label 2019) at 2–3; PX 1203 (Hikma 2019 Proposed Label) at 2; PX 1209 (DRL 2020 Proposed Label) at 2–3.

330. The absence of a warning would be conspicuous to clinicians because the prescribing information for Lovaza and several fibrates contain such a warning. Trial Tr. 407:17–25 (Budoff Direct) ("So, in all the other therapies, the fibrates, Lovaza, there is a warning about LDL rise in the Warnings and Precautions section of those labels. Here there is no such warning, and a doctor who is treating severe hypertriglyceridemia would know that. This would be common knowledge of the effects of the other agents and the warnings that go with the other agents, and so

the absence of that warning is important for physicians to understand."); *see also* Trial Tr. 341:1–16 (Budoff Re-Direct). And physicians who treat patients with severe hypertriglyceridemia would be intimately familiar with the effects of other available drugs (niacin, fibrates, and Lovaza). Trial Tr. 659:11–18 (Sheinberg Cross).

331. For example, the 2007 version of the LOVAZA label stated in the "Precautions" section that "[i]n some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels." PX 566/DX 1578 (Lovaza 2007 Label) at 1. The label further instructed clinicians that "LDL-C levels should be monitored periodically during Lovaza therapy." *Id*. Furthermore, the VASCEPA Medical Review, which Dr. Sheinberg opined contains information that a physician would bring to bear in reading Defendants' labels (*see supra* § IV.A) describes the concerning rise in LDL-C associated with Lovaza and distinguishes the effects achieved with Vascepa. PX 289 (VASCEPA FDA Medical Review) at 14 (explaining "the only other FDA approved omega-3 fatty acid product (Lovaza)" has "four areas of potential safety concern," beginning with "increases in LDL-C").

332. Additionally, as described above (*see supra* § II.C.1) the labels of several fibrates warn of a rise in LDL-C. *See* PX 964 (Lopid PDR 1990) at 2 ("Patients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil. In some patients with high triglyceride[] levels, treatment with gemfibrozil is associated with a significant increase in LDL-cholesterol."); *see also* PX 825 (Lopid PDR 2004) at 3, 2556 (same); PX 966 (Tricor PDR) at 4, 529, Tbl. 2 (reporting that in patients with TG levels from 500 to 1500 mg/dL, LDL-C increased by 45% from baseline).

333. Together, these sections of Defendants' labeling encourage, recommend, promote, or suggest toclinicians to administer Defendants' ANDA Products, with the intent to reduce patients' TG levels without substantially increasing LDL-C. Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered. *See* Trial Tr. 402:3–409:6 (Budoff Direct); *see also* Mathers Dep. 154:5–9, 154:11–12 ("[s]ome prescribers will understand

the Vascepa labeling to tell them that they can administer Vascepa to their severely hypertriglycerdemic patients so as to reduce triglycerides without raising LDL-C").

334. The intended result, a reduction in TGs without raising LDL-C will be met in a majority of cases. *E.g.*, Trial Tr. 398:9–20 (Budoff Direct); Trial Tr. 667:18-20 (Sheinberg Cross); Trial Tr. 1167:1–12 (Fisher Cross); *see also* PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; PX 289 (VASCEPA FDA Medical Review) at 58; PX 807 (MARINE CSR) at 11, 81.

335. Finally, as Mr. Mathers admitted, administering VASCEPA to a patient to reduce TGs without raising LDL-C is consistent with the approved indication. Mathers Dep. 182:12–24. That is to say, administering VASCEPA to reduce TGs without raising LDL-C is not an "off-label" use. Mathers Dep. 156:11–18; *see also* Trial Tr. 1345:10–25 (Peck Direct). A manufacturer cannot advertise a drug beyond its scope of approval, Trial Tr. 1348:16–19 (Peck Direct); Mathers Dep. 158:25–159:3, and Amarin has been permitted to promote VASCEPA for its ability to lower TGs in severely hypertriglyceridemic patient populations *without raising LDL-C*. Trial Tr. 1350:19–23 (Peck Direct); Trial Tr. 112:21–117:7 (Ketchum Direct); Trial Tr. 1349:12–1350:23 (Nicholson Direct). Amarin's ability to promote Vascepa to reduce TGs without raising LDL-C is confirmation that Vascepa is approved as safe and effective for this use.

336. Thus, the labeling taken in its entirety, establishes that Vascepa is safe and effective to reduce TGs without raising LDL-C. The intent prong for inducement is established when "the label, *taken in its entirety* . . . recommend[s] or suggest[s] *to a physician*" that the drug used in the claimed method of treatment is safe and effective for causing the effects described in the patent claims. *Bayer*, 676 F.3d at 1324 (emphases added).

337. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—"without substantially increasing LDL-C" as required, for example, by Claim 1 of the '728 Patent.

2. "to effect a reduction . . . in apo B"

338. Several asserted claims further require administration of the claimed pharmaceutical composition "to effect a statistically significant reduction . . . in apolipoprotein B" or "to effect a reduction in apolipoprotein B." PX 22 ('715 Patent) Claim 14; PX 25 ('677 Patent) Claim 8.

339. Similar to the analysis above concerning LDL-C, Defendants' will induce infringement of the limitations concerning apo B because clinicians will read Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to reduce TGs in severely hypertriglyceridemic patients and in conjunction with the TG reduction,"effect a statistically significant reduction . . . in apolipoprotein B." Trial Tr. 427:9–19 (Budoff Direct). Trial Tr. 1407:11–15 (Peck Direct) (FDA "approved Vascepa for the treatment of [severe] hypertriglyceridemia while reducing apo B. This is clear in the label."). Here, too, the Clinical Studies section of the labeling reports the statistically significant decrease in apo B resulting from administration of VASCEPA in Table 2 and then calls out that in text below that the drug reduced both median TG and apo B. The labeling thusconveys to physicians both the clinical significance of the drug's effect on apo B and the fact that such a reduction will occur in their patients in clinical practice. Trial Tr. 427:15–428:5 (Budoff Direct); *see also id.* at 1408:19–22 (Peck Cross) (FDA "interpreted this information and it called out that decrease. And so FDA approved this label, it approved this drug for the treatment of hypertriglyceridemia while reducing apo B"); Mathers Dep. 134:10–13 (Clinical Studies section of the labeling identifies Apo B among the "relevant parameters to measure on a routine basis and to monitor").

340. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling, like the same table in the Clinical Studies section of VASCEPA's labeling, reports that 4 g per day of EPA resulted in a 9% reduction in apo B compared to placebo. Table 2 further states that the 9% reduction in apo B was statistically significant by reporting a p-value of less than 0.05. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 427:9–22 (Budoff Direct). The callout in the Clinical

Studies section reflects FDA's judgment that VASCEPA's effect on apo B was relevant to the treatment of severe hypertriglyceridemia. Trial Tr. 1408:16–22 (Peck Direct). Mr. Mathers likewise acknowledged that FDA specifically approved the statements in the Clinical Studies section concerning apo B effects. Mathers Dep. 187:2–10. The statement below Table 2 establishes that FDA determined that Vascepa is safe and effective to reduce triglycerides in adult patients with severe hypertriglyceridemia while also lowering apo B. Trial Tr. 1351:15–19 (Peck Direct).

341. By instructing clinicians that 4 g per day of icosapent ethyl has been shown to cause a statistically significant reduction in TGs *and* apo B when administered to adult patients with severe hypertriglyceridemia, the Clinical Studies section of Defendants' labeling encourages, recommends, promotes, or suggests that clinicians administer Defendants' ANDA Products with the intent to effect a statistically significant reduction in TGs while having the additional beneficial effect of a statistically significant reduction in apo B. Table 2 further confirms that physicians will observe such a reduction in their patients. Mr. Mathers admitted that the Clinical Studies section shows that the majority of patients could see a reduction in TGs while also experiencing a reduction in apo B. Mathers Dep. 155:16–156:3. Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling. Trial Tr. 427:9–428:9 (Budoff Direct); *see also* Trial Tr. 658:17–19 (Sheinberg Cross) (apo B is "very important" to his clinical practice). Mr. Mathers acknowledged that some physicians might read the VASCEPA labeling to understand that they can treat their severely hypertriglyceridemic patients with VASCEPA so as to reduce triglyceride levels and lower apo B levels. Mathers Dep. 154:23–155:2, 155:4–15.

342. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a statistically significant reduction . . . in apolipoprotein B" as required by Claim 14 of the '715 Patent. PX 22 ('715 Patent) at 22, Claim 14.

D. Defendants' Labels Will Induce Clinicians to Administer Defendants' ANDA Products to Severely Hypertriglyceridemic Patients as Monotherapy Without Concurrent Administration of Other Lipid-Lowering Drugs Like Statins

343. This limitation requires administration of the claimed pharmaceutical composition to a patient "who does not receive concurrent lipid altering therapy." PX 21 ('728 Patent) at 21–22 Claims 1,16; *see also* PX 22 ('715 Patent) at 22, Claim 14 ("who does not receive a concurrent lipid altering therapy"). The Court construed the term "concurrent lipid altering therapy" to mean "a medication to alter lipid levels in a subject whereby the medication is administered concurrently / concomitantly with the administration of a pharmaceutical composition comprising ethyl eicosapentaenoate." Claim Construction Order at 5–7 (ECF No. 135); Trial Tr. 409:21–410:6 (Budoff Direct). Statins are an example of a "medication to alter lipid levels." *See* Trial Tr. 412:1–6, 414:1–20 (Budoff Direct) (identifying statins as concurrent lipid altering therapies).

344. Based on the Court's construction, a clinician who administers Defendants' ANDA Products to a patient who is not on another lipid altering medication (*e.g.*, a statin) will directly infringe this limitation.

345. Defendants will induce infringement of this limitation because clinicians will read the Indications and Usage, Dosage and Administration, and Clinical Studies sections of Defendants' labeling as encouraging, promoting, recommending, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia who do not receive concurrent lipid altering therapy. Trial Tr. 409:7–415:11 (Budoff Direct) (full discussion of monotherapy limitation of the '728 Patent); Trial Tr. 1352:12–20 (Peck Direct). *Cf.* Mathers Dep. 66:24–67:4 (agreeing that "Defendants' proposed labeling recommends, encourages, and instructs administration to patients with severe hypertriglyceridemia whether or not they are receiving lipid-altering medication . . .").

346. ***Indications and Usage Section.*** The Indications and Usage section of Defendants' label, like the same section in the VASCEPA label, states that Defendants' ANDA products will be indicated "as an adjunct to diet to reduce triglycerides (TG) in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." Joint Stipulations of Fact ¶¶ 200, 212, 224 (ECF No. 324). The

Indications and Usage section does not require or otherwise reference the use of any other medication with Defendants' ANDA Products. The Indications and Usage section thus instructs the use of Defendants' ANDA Products as a mono-pharmacotherapy, without coadministration of any other drug. Trial Tr. 410:11–25 (Budoff Direct) ("So you [] see the MARINE indication literally says as an adjunct to diet to reduce triglyceride levels. So diet is not considered concurrent lipid altering therapy. The Court construed that that's a medication. So this is literally advocating for Vascepa to be used as monotherapy without concurrent -- it's not requiring concurrent lipid altering therapy.").

347. If a drug is approved *only* for use in combination with another therapy or therapeutic modality, FDA requires an applicant to include a statement to that effect in the Indications and Usage section of the drug's label. *See* PX 573 (FDA Guidance: Indications and Usage) at 7, 12. Here, as Defendants' expert Mr. Mathers admitted, it is within the scope of the approved indication to administer VASCEPA to someone not on concurrent lipid altering therapy. Mathers Dep. 67:5–9, 67:11–14, 67:16–20, 67:22–24, 69:23–70:3, 70:5; *see also* Mathers Dep. 70:16–20, 70:22 (a physician could follow the label to prescribe VASCEPA).

348. Without a statement referring to another medication in the indication, a clinician reading Defendants' labeling will understand that FDA has determined that Defendants' ANDA Products, when used in combination with diet, are safe and effective to reduce TGs in adult patients with severe hypertriglyceridemia without coadministration of any other medication, including any lipid-altering therapy, like statins. *See* Trial Tr. 410:11–25 (Budoff Direct).

349. ***Dosage and Administration Section.*** This encouragement is reinforced by the Dosage and Administration sections of Defendants' proposed labeling. When FDA has determined that a drug should be used with another drug to "minimize toxicity" or "enhance effectiveness," or "if [a] drug has been demonstrated to be effective only in combination with another therapy," the Dosage and Administration section of the drug's label "should identify and describe any recommended concomitant medications" or "therap[ies]." PX 572 (FDA Guidance: Dosage and Administration) at 8.; Trial Tr. 1352:21–1354:3 (Peck Direct).

350. The Dosage and Administration section of Defendants' labeling, like the same section in VASCEPA's labeling, does not "identify" or "describe" any "recommended concomitant medications." *See* PX 1186 (VASCEPA Label 2019) at 2; PX 1203 (Hikma 2019 Proposed Label) at 2; PX 1209 (DRL 2020 Proposed Label) at 2; Trial Tr. 1355:3–6 (Peck Direct).

351. ***Clinical Studies Section.*** The Clinical Studies section of Defendants' proposed labels further encourages clinicians to administer EPA without a concurrent lipid altering therapy. Under FDA regulations, "the Clinical Studies section of labeling must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively." PX 776 (FDA Guidance: Clinical Studies Section) at 5; Trial Tr. 1332:10–1333:7 (Peck Direct).

352. In describing MARINE, the Clinical Studies section states that only "[t]wenty-five percent of patients" in the study "were on concomitant statin therapy." PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9.

353. Clinicians appreciate from the clinical study description that the remaining 75% of patients in the study described in the Clinical Studies section were not on concurrent lipid altering therapy (e.g., statins). Trial Tr. 1413:8–18 (Peck Direct); *see also* Mathers Dep. 68:1–5, 68:7–15 ("I believe the number was, were on statins and suggesting that 75 percent were not . . . in that study population.").

354. Clinicians also understand that EPA was approved for use without any concomitant medication (including statins) because FDA did not believe the effectiveness (or safety) of EPA in reducing TGs in adult patients with severe hypertriglyceridemia was dependent on concomitant statin therapy. Trial Tr. 412:12–414:15 (Budoff Direct) (describing how the clinical studies section assures him EPA is safe and effective as monotherapy in certain patients); Mathers Dep. 75:23–76:2, 76:4–15, 76:17–18 (a physician would understand from the Clinical Studies section that VASCEPA can be safely and effectively administered without regard to concurrent statin therapy); Trial Tr. 1413:8–18 (Peck Direct) (FDA determined that "Vascepa is safe and effective as a monotherapy" (i.e. a one-drug therapy used as an adjunct to diet) "to reduce triglycerides in adult

patients with severe hypertriglyceridemia."). For this reason, as Mr. Mathers admitted, the Clinical Studies section affirmatively instructs that Vascepa can be safely and effectively administered to patients without regard to concurrent statin therapy. Mathers Dep. 76:20–25.

355. Furthermore, the Clinical Studies section of Defendants' labels, like the same section in the VASCEPA label, instructs physicians that, when administered to adult patients with severe hypertriglyceridemia, 4 g per day of icosapent ethyl reduced patients' TG levels while reducing VLDL-C and apo B and without raising LDL-C. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9. This also instructs clinicians that they may administer Defendants' ANDA Products to adult patients with severe hypertriglyceridemia without causing adverse effects in the patients' other major lipoprotein lipid levels that would require coadministration of another lipid-altering medication (*e.g.*, statins) to treat or manage.

356. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice will be used—by patients who "do[] not receive concurrent lipid altering therapy" as required by Claim 1 of the '728 Patent (PX 21). Trial Tr. 409:7–415:11 (Budoff Direct) (full discussion of monotherapy limitation of the '728 Patent).

E. Clinicians Prescribing Vascepa or One of Defendants' ANDA Products to Treat Severely Hypertriglyceridemic Patients Will Directly Infringe the Asserted Claims

357. With respect to direct infringement, as explained extensively above, clinicians will follow the claimed method when treating their severely hypertriglyceridemic patients with VASCEPA or one of Defendants' ANDA Products.

358. Dr. Budoff testified that clinicians' intentions when administering VASCEPA are to (1) administer VASCEPA long term, for at least 12 weeks, Trial Tr. 390:1–391:15 (Budoff Direct), (2) administer VASCEPA to achieve certain lipid effects in his patients including a reduction in TG levels, no increase in LDL-C, and a reduction in apo B, Trial Tr. 399:4–12 (Budoff Direct), and (3) administer VASCEPA as a monotherapy, where doing so is appropriate, Trial Tr.

411:5–412:6 (Budoff Direct). *See also* Trial Tr. 390:8–10; 426:9–11 (Budoff Direct)(confirming other physicians have the same intent). Defendants' expert witnesses agreed. Trial Tr. 696:16–19; 669:4–17 (Sheinberg Cross); Trial Tr. 851:2–5 (Heinecke Cross).

359. Moreover, the intended lipid effects (reduction in TG, no increase in LDL-C, and a reduction in apo B) will in fact be achieved. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; PX 289 (VASCEPA Medical Review) at 58; PX 807 (MARINE CSR) at 11, 79, 81.

360. Importantly, Defendants do not appear to be disputing that some physicians will directly infringe the Asserted Claims, nor could they. Dr. Sheinberg's testimony was limited to an analysis of induced infringement. *See* Trial Tr. 602:4–12 (Sheinberg Direct) (providing only the standard for induced infringement); *but see* Trial Tr. 361:4–7, 15–18 (Budoff Direct) (explaining that Dr. Budoff was instructed on and applied the standard for direct infringement). Therefore Amarin has met its burden of establishing direct infringement.

F. Defendants Will Induce Infringement of Each of the Asserted Claims

361. The main issues relating to infringement that are in dispute between the parties have been addressed in Sections XI.B–D above. The remaining limitations of the Asserted Claims have in large part either been stipulated to or do not appear to be in dispute. Amarin addresses each of the Asserted Claims in turn below.

362. As established through sections IX. B–D, all limitations of the Claim 1 of the '728 Patent have been met. Trial Tr. 364:13–17 (Budoff Direct) ("Q. Would somebody following the labeling of the Vascepa product follow every element of claim 1 of the 728 Patent? A. Yes. The label encourages these steps to be taken and all of these elements to be met when prescribing these therapies.").

1. Defendants Will Induce Infringement of Claim 1 of the '728 Patent

363. Claim 1 of the '728 Patent is an independent claim. It recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who does not receive concurrent lipid altering therapy comprising:

> administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

PX 21 ('728 Patent) at 21.

364. The 12 week, TG reduction, LDL-C, and concurrent lipid altering therapy limitations that appear in Claim 1 have been addressed in detail above. *See supra* ¶¶ 296–356.

365. Defendants have stipulated that their products, as well as VASCEPA, contain a "pharmaceutical composition." Joint Stipulations of Facts, ¶¶ 204, 216, 228 (ECF No. 324); *see* Trial Tr. 363:19–364:4 (Budoff Direct). In addition, Defendants have stipulated that the "pharmaceutical composition" in their ANDA Products, as well as in VASCEPA, comprises "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate[,] and substantially no docosahexaenoic acid or its esters." Joint Stipulations of Fact, ¶¶ 205, 217, 229 (ECF No. 324); *see* Trial Tr. 363:19–364:4 (Budoff Direct).

366. At trial, Defendants did not appear to challenge the following claim limitations from the '728 Patent (PX 21), Claim 1, (which are also representative of the same or similar claim limitations in the other Asserted Patents):

- "[a] method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"
- "administering orally to the subject about 4 g per day of a pharmaceutical composition"
- "compared to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy"

367. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will induce infringement of these limitations in Claim 1 of the '728 Patent.

a) "A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"

368. This limitation requires administration of the claimed pharmaceutical composition to a patient with a fasting baseline TG level between 500 mg/dL and 1500 mg/dL. As an initial matter, Defendants' infringement expert, Dr. Sheinberg, conceded that the indication and usage section encourages doctors to administer VASCEPA to patients to reduce triglyceride levels in subjects having fasting baseline triglyceride levels of 500 mg/dL or higher. Trial Tr. 656:17–22 (Sheinberg Cross); *see also* Mathers Dep. 64:23–65:4 (Defendants' labeling encourages administration of a 4 g daily dose as an adjunct to diet to reduce triglycerides in adult patients with severe hypertriglyceridemia).

369. Defendants will induce infringement of this limitation because clinicians will read the Indications and Usage, Dosage and Administration, and Clinical Studies sections of Defendants' labeling as encouraging, promoting, recommending, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia, *i.e.*, patients who have fasting baseline TG levels ≥ 500 mg/dL to about 1500 mg/dL. Trial Tr. 364:18–365:7 (Budoff Direct). In addition, clinicians will actually be induced to administer Defendants' ANDA products to a patient with a fasting baseline TG level within this range.

370. ***Indications and Usage Section.*** The Indications and Usage section of Defendants' labeling, like the same section in VASCEPA's labeling, states that Defendants' ANDA products will be indicated "as an adjunct to diet to reduce triglycerides (TG) in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia" an indication that necessarily includes "subjects having a fasting baseline triglyceride level of 500 mg/d[L] to about 1500 mg/d[L]" as stated in Claim 1. Joint Stipulations of Fact ¶¶ 200, 212, 224 (ECF No. 324); Trial Tr. 365:8–18 (Budoff Direct).

371. ***Dosage and Administration Section.*** The term "baseline," as used to describe a lipid measurement, refers to a measurement done before or at the start of therapy. The Dosage and Administration section of Defendants' labeling instructs clinicians to "[a]ssess lipid levels before initiating therapy." PX 1186 (VASCEPA Label 2019) at 2; PX 1203 (Hikma 2019 Proposed Label) at 2; PX 1209 (DRL 2020 Proposed Label) at 2. That pre-initiation assessment establishes a "baseline" triglyceride level. Trial Tr. 329:25–330:5 (Budoff Direct) ("So to actually assess a patient's baseline, where they're starting with their triglycerides, we do it in the fasting state so after I treat a patient, be it with diet and exercise, or be it with a drug, I can then follow that value in the fasting state to see what the net effect was of my treatment."). Clinicians understand that the baseline level is measured in the fasting state. *See* PX 989 (ATP-III) at 91; DX 1876 (ATP-III) at 86 ("[a] lipoprotein profile involving measurement of triglycerides . . . requires a 9- to 12- hour fast."); Trial Tr. 658:3–5 (Sheinberg Cross)("typically when lipids are measured it's after a 12-hour fast").

372. ***Clinical Studies Section.*** In addition, the Clinical Studies section of Defendants' labeling instructs physicians that FDA determined that EPA 4 g per day effectively reduces triglycerides when administered for 12 weeks to "[p]atients whose baseline TG levels were between 500 and 2,000 mg/d[L]." PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 365:22–3662 (Budoff Direct) ("Q. Is there anything in the clinical study section relevant to our opinion that the first element of claim 1 of the 728 patent is met? A. Yes. I mean, this, again, is in patients with severe hypertriglyceridemia, and it demonstrates that use if the drug will reduce triglycerides here by an average of 33 percent.").

373. Thus, based on the instructions in Defendants' labels, Defendants intend for their products to be—and in clinical practice they will be—administered in patients with a fasting baseline triglyceride level of 500 mg/dL to 1500 mg/dL.

b) "administering orally to the subject about 4 g per day of a pharmaceutical composition"

374. This limitation requires oral administration to patients of about 4 g per day of the claimed pharmaceutical composition.

375. As an initial matter, Defendants' experts have not contested that Defendants' labels will encourage clinicians to use Defendants' ANDA Products by "administering orally to the subject about 4 g per day of [the] pharmaceutical composition" described in the Asserted Claims. Trial Tr. 657:6-21 (Sheinberg Cross) ("Q. And you would agree that the statement in the dosage and administration section instructions clinicians to administer 4 grams per day of Vascepa in patients with severe hypertriglyceridemia? A. Yes. … Q. You agree that the statement in the dosage and administration section instructs clinicians to administer Vascepa orally? A. Yes.").

376. This Court previously interpreted the term "administering orally" as "the doctor prescribing the medication, and the medication is delivered into the patient's body at the doctor's direction." Claim Construction Order, at 8 (ECF No. 135). The Court's claim construction recognizes that Defendants' ANDA Products are available only with a prescription from a clinician. Any administration of the medication is impossible without the clinician prescribing the medication for and providing instructions to the patient, and all administration of Defendants' ANDA Products is therefore done under the direction of the clinician who writes the prescription. Trial Tr. 416:7–22 (Budoff Direct).

377. Defendants will induce infringement of this limitation because clinicians will read the Description, Dosage and Administration, Patient Counseling Information, and Clinical Studies sections of Defendants' labeling as encouraging, promoting, recommending, or suggesting to clinicians to prescribe 4 g per day of Defendants' ANDA products to patients and to direct the patients to take the 4 g per day orally. Trial Tr. 415:15–419:25 (Budoff Direct). A clinician who prescribes Defendants' ANDA Products for the stated dosage amount (4 g per day) and directs a patient to take the medication will directly infringe this limitation.

378. ***Dosage and Administration Section.*** The Dosage and Administration section instructs that the daily dose of Defendants' 1 g icosapent ethyl capsules is 4 g per day taken as 2 capsules twice daily with food. In addition, "[p]atients should be advised to swallow icosapent ethyl capsules whole." PX 1186 (VASCEPA Label 2019) at 2; PX 1203 (Hikma 2019 Proposed Label) at 2; PX 1209 (DRL 2020 Proposed Label) at 2; Trial Tr. 418:17–22 (Budoff Direct) ("Under 2.2, dosage and administration, the daily dose of Vascepa is 4 grams per day, and then advise patients to swallow whole and take it with food. Both of those imply -- the only way you can swallow it or take it with food is an oral administration."); Trial Tr. 657:18–21 (Sheinberg Cross).

379. ***Patient Counseling Information Section.*** The Patient Counseling Information section of Defendants' labeling, like the same section in VASCEPA's labeling, further encourages clinicians to "advise[]" patients to "not alter [Defendants'] capsules in any way and to ingest intact capsules only" and "[i]nstruct patients to take [Defendants' ANDA Products] as prescribed." PX 1186 (VASCEPA Label 2019) at 11–12; PX 1203 (Hikma 2019 Proposed Label) at 8; PX 1209 (DRL 2020 Proposed Label) at 9–10. By communicating to clinicians that they should instruct their patients to swallow the capsules whole, Defendants' labeling instructs, advises, and encourages physicians to prescribe Hikma's ANDA Product to their patients and then direct the patients on the manner in which the medication should be delivered into their bodies—orally.

380. ***Clinical Studies Section.*** Additionally, the Clinical Studies section of Defendants' labeling, like the same section in VASCEPA's labeling, instructs clinicians that "icosapent ethyl 4 grams per day" was effective to reduce TGs (while also reducing apo B and without increasing LDL-C). PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9.

381. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be—and in clinical practice will be—"administer[ed] orally to the subject about 4 g per day of a pharmaceutical composition" as required by Claim 1 of the '728 Patent.

c) "compared to a second subject"

382. The Court construed the term "compared to having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy" as having its plain and ordinary meaning. Ultimately, this term simply refers to "a comparison between what happens when the treatment is administered versus what would otherwise happen to a second subject" who does not receive treatment. Claim Construction Order, at 12–13 (ECF No. 135). This term "defines the magnitude of the lipid effect or avoidance of the undesirable lipid effects" and "the clinical data in the [patent file history] . . . supports . . . the term's plain and ordinary meaning." *Id.* at 13.

383. The "compared to" claim language is linked to the "to effect" claim language. The "to effect" limitation requires that the effect actually occur and the "compared to" limitation instructs how to determine that the claimed effect has occurred. Trial Tr. 394:10–395:16 (Budoff Direct).

384. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia to reduce the patients' TG levels without substantially increasing LDL-C "compared to a second subject having a fasting baseline triglyceride level of 500 mg/dL to about 1500 md/dL who has not received the pharmaceutical composition and a concurrent lipid altering therapy." Trial Tr. 394:1–9 (Budoff Direct).

385. ***Clinical Studies Section.*** As noted previously, the Clinical Studies section in Defendants' labeling reports the results of a placebo-controlled study in which investigators administered 4 g per day of EPA to 76 patients with severe hypertriglyceridemia and 4 g per day of a placebo (*i.e.*, a product with no icosapent ethyl) to 75 different patients with severe hypertriglyceridemia for a period of 12 weeks. Thus, during the course of the study these 75 subjects did not receive the "pharmaceutical composition" described in Claim 1 of the '728 Patent—96% EPA and substantially no DHA. *See* PX 1186 (VASCEPA Label 2019) at 11; PX

1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9. And many of these subjects also did not receive "a concurrent lipid altering therapy" as required by Claim 1 of the '728 Patent. PX 1186 (VASCEPA Label 2019) at 11 (providing that 75% of the subjects in the study were not on concurrent statin therapy); PX 1203 (Hikma 2019 Proposed Label) at 7–8 (same); PX 1209 (DRL 2020 Proposed Label) at 8–9 (same). Accordingly, the placebo group consists of "second subject[s] having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who have not received the pharmaceutical composition and a concurrent lipid altering therapy," as required in Claim 1. *See* Trial Tr. 396:15–23 (Budoff Direct).

386. Table 2 in the Clinical Studies section of Defendants' labeling reports the results of that study, including by summarizing the median percent change in various lipid levels in the group that received EPA compared to baseline and compared to placebo. This information provides a comparison of the lipid effects experienced by this group of "second subject[s]" to the lipid effects experienced by the group who received the icosapent ethyl treatment. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9.

387. The Clinical Studies section of Defendants' labeling (and VASCEPA's labeling) instructs clinicians that icosapent ethyl 4 g per day reduces TGs without substantially raising LDL-C compared to placebo control when administered for 12 weeks, and thereby encourages clinicians to administer Defendants' ANDA Products with the intent to reduce TGs in their severely hypertriglyceridemic patients while having the additional beneficial effect of not substantially raising those patients' LDL-C levels (compared to what they would have been with no treatment). Furthermore the Clinical Studies section demonstrates that clinicians will in fact observe such results in their patients.

388. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—to effect a reduction in triglycerides without substantially increasing LDL-C "compared to a second subject having a fasting baseline triglyceride level of 500 mg/d[L] to about 1500 mg/d[L]

who has not received the pharmaceutical composition and a concurrent lipid altering therapy," as required by Claim 1 of the '728 Patent. PX 21 ('728 Patent) at 21.

2. Defendants Will Induce Infringement of Claim 16 of the '728 Patent

389. Claim 16 of the '728 Patent is a dependent claim that depends from Claim 1 of the '728 Patent. As a dependent claim, Claim 16 incorporates the limitations in Claim 1.

390. In addition, Claim 16 of the '728 Patent recites:

> The method of claim 1, wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined.

PX 21 ('728 Patent) at 22.

391. For the reasons discussed in Paragraphs 296–356 and 363–388 above, Defendants will induce infringement of all limitations in Claim 1 of the '728 Patent. Trial Tr. 420:19–25 (Budoff Direct).

392. Claim 16 adds only one additional limitation: "wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined." PX 21 ('728 Patent) at 22.

393. Defendants have stipulated that their ANDA Products will meet the only limitation that Claim 16 adds to Claim 1. *See supra* Joint Stipulations of Fact ¶ 206 (ECF No. 324).

394. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—as required by Claim 16 of the '728 Patent. Trial Tr. 421:7-15 (Budoff Direct) ("Q. So just to sum up, would the labeling -- Vascepa labeling encouraging -- encourage clinicians to follow each step of the method claimed by claim 16 of the '728 Patent? A. Yes. For all the reasons I've previously stated, physicians will --following the label will meet all of these elements.")

395. Clinicians will perform each of the method steps in Claim 16 of the '728 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information. Trial Tr. 420:19–421:12 (Budoff Direct).

3. Defendants Will Induce Infringement of Claim 1 of the '652 Patent

396. Claim 1 of the '652 Patent is an independent claim. Claim 1 of the '652 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/d[L] to about 1500 mg/d[L]comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline.

PX 26 ('652 Patent) at 22.

397. Defendants will induce infringement of the disputed limitations in Claim 1 of the '652 Patent depicted in the following chart, which are the same or similar to the limitations in Claim 1 of the '728 Patent:

"A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"	*See supra* ¶¶ 368–373
"administering orally to the subject"	*See supra* ¶¶ 374–381
"about 4 g per day"	*See supra* ¶¶ 374–381
"of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters"	*See supra* ¶ 365
"for a period of about 12 weeks"	*See supra* ¶¶ 296–356, 364
"to effect a reduction in triglycerides"	*See supra* ¶¶ 382–388
"without substantially increasing LDL-C"	*See supra* ¶¶ 382–388

See Trial Tr. 422:8–20 (Budoff Direct).

398. Claim 1 of the '652 Patent adds one additional claim limitation not yet addressed: "to effect a reduction in triglycerides without substantially increasing LDL-C *compared to baseline.*" PX 30 ('560 Patent) at 22 (emphasis added).

399. This limitation is similar to the limitation in Claim 1 of the '728 Patent that requires administration of the pharmaceutical composition "to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject." The only difference is that in Claim 1 of the '652 Patent the effect is measured "compared to baseline," rather than as "compared to a second subject" (as in Claim 1 of the '728 Patent (PX 21)). *See supra* ¶¶ 382–388.

400. Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitation in Claim 1 of the '652 Patent. Furthermore, Defendants' proposed labeling will induce clinicians to infringe the remaining limitations in Claim 1 of the '652 Patent.

401. The claim term "compared to" simply refers to "a comparison between what happens when treatment is administered versus what would otherwise happen." Claim Construction Order at 12–13 (ECF No. 135). In essence, the "compared to" term "defines the magnitude of the lipid effect or avoidance of the undesirable lipid effects." *See also supra* ¶ 382.

402. ***Clinical Studies Section.*** As explained in ¶¶ 187–189, the Clinical Studies section of Defendants' labeling, reports the results of a placebo-controlled study in which investigators administered 4 g per day of icosapent ethyl to 76 patients with severe hypertriglyceridemia and 4 g per day of a placebo to 75 different patients with severe hypertriglyceridemia for a period of 12 weeks. Table 2 in the Clinical Studies section reports the results of that study, including by summarizing the median percent change in various lipid levels in the group that received icosapent ethyl, compared to baseline and compared to placebo. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 423:16–28 (Budoff Direct) ("So in the Table 2, can you see under Vascepa, it says the word baseline. These are the changes that are seen compared to baseline.").

403. The label therefore conveys to clinicians the degree to which icosapent ethyl beneficially alters lipid levels in patients with severe hypertriglyceridemia compared to their baseline levels. Table 2 instructs clinicians that administration of icosapent ethyl 4 g per day for 12 weeks led to a median 27% reduction in TG levels from baseline and a median 5% reduction

in LDL-C levels from baseline. Defendants' labeling thereby encourages clinicians to administer Defendants' ANDA Products to severely hypertriglyceridemic patients with the intent of reducing TGs without raising LDL-C compared to baseline. Trial Tr. 423:16–28 (Budoff Direct) ("So to effect a reduction in triglycerides, the change was 27 percent compared to baseline. Two, without increasing LDL-C, there was a minus five percent, there was decrease in LDL-C compared to baseline. So these elements will be met when physicians follow the label."). Moreover the clinical studies section demonstrates that patients will actually achieve the reported results. Trial Tr. 423:24–424:7 (Budoff Direct).

404. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline," as required by Claim 1 of the '652 Patent. PX 26 ('652 Patent) at 22.

* * *

405. Clinicians will perform each of the method steps in Claim 1 of the '652 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information. Trial Tr. 424:8–11 (Budoff Direct).

4. Defendants Will Induce Infringement of Claim 1 of the '677 Patent

406. Claim 1 of the '677 Patent is an independent claim. Claim 1 of the '677 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/d[L] to about 1500 mg/d[L] comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of at least about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control.

PX 25 ('677 Patent) at 21.

407. As discussed above, Defendants will induce infringement of the disputed limitations in Claim 1 of the '677 Patent depicted in the following chart, which are the same or similar to the limitations in Claim 1 of the '728 Patent:

"A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"	*See supra* ¶¶ 368–373
"administering orally to the subject"	*See supra* ¶¶ 374–381
"about 4 g per day"	*See supra* ¶¶ 374–381
"of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters"	*See supra* ¶ 365
"for a period of about 12 weeks"	*See supra* ¶¶ 296–356, 364
"to effect a reduction in triglycerides"	*See supra* ¶¶_382–388
"without substantially increasing LDL-C"	*See supra* ¶¶ 382–388

Trial Tr. 424:22–425:5 (Budoff Direct).

408. Claim 1 of the '677 Patent adds one additional claim limitation not yet addressed. This limitation is similar to the limitation in Claim 1 of the '728 Patent that requires administration of the pharmaceutical composition "to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second subject." The only difference is that in Claim 1 of the '677 Patent the effect is measured "compared to placebo control," rather than as "compared to a second subject" (as in Claim 1 of the '728 Patent). *See supra* ¶¶ 382–388.

409. Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitation in Claim 1 of the '677 Patent. Furthermore, Defendants' proposed labeling will induce clinicians to infringe the remaining limitations in Claim 1 of the '677 Patent. Trial Tr. 425:8–24 (Budoff Direct).

410. The placebo group in the clinical study reported in the Clinical Studies section of Defendants' labeling, like the section in VASCEPA's labeling, is a group of subjects who received a placebo rather than the studied treatment (4 g per day of icosapent ethyl). *See supra* ¶ 189. The data reported in the clinical studies section includes data compared to placebo control. Specifically, a median 33% reduction in TGs and a median 2% reduction in LDL-C when compared to placebo control (*i.e.*, compared to the 75 patients who did not receive the treatment). PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9. Trial Tr. 425:8–426:22 (Budoff Direct).

411. Thus, the Clinical Studies section of Defendants' labeling (and VASCEPA's labeling) instructs clinicians that icosapent ethyl 4 g per day reduces TGs without substantially raising LDL-C compared to placebo control when administered for 12 weeks. Clinicians will read the Defendants' labeling as encouraging, recommending, promoting, or suggesting that clinicians administer Defendants' ANDA Products with the intent and expectation that they will reduce TGs in their severely hypertriglyceridemic patients while having the additional beneficial effect of not substantially raising those patients' LDL-C levels (compared to what they would have been with no treatment). Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling. Trial Tr. 425:8–426:16 (Budoff Direct).

412. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control" as required by Claim 1 of the '677 Patent. PX 25 ('677 Patent) at 21.

* * *

413. Clinicians will perform each of the method steps in Claim 1 of the '677 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information. Trial Tr. 426:17–22 (Budoff Direct).

5. Defendants Will Induce Infringement of Claim 8 of the '677 Patent

414. Claim 8 of the '677 Patent is a dependent claim that depends from Claim 1 of the '677 Patent. As a dependent claim, Claim 8 incorporates the limitations in Claim 1.

415. In addition, Claim 8 of the '677 Patent recites:

> The method of claim 1, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of at least about 12 weeks to effect a reduction in apolipoprotein B compared to placebo control.

PX 25 ('677 Patent) at 22.

416. As a dependent claim, Claim 8 of the '677 Patent incorporates the limitations of the claim from which it depends, Claim 1 of the '677 Patent.

417. For the reasons discussed at Paragraphs 406–413 above, Defendants will induce infringement of all limitations in Claim 1 of the '677 Patent.

418. Claim 8 of the '677 adds only one additional limitation: "to effect a reduction in apolipoprotein B compared to placebo control"

419. Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe this remaining limitation in Claim 8 of the '677 Patent. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitation in Claim 8 of the '677 Patent for the reasons described below.

420. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA products to patients with severe hypertriglyceridemia "to effect a reduction in apolipoprotein B compared to placebo control." Trial Tr. 427:9–19 (Budoff Direct).

421. ***Clinical Studies Section.*** As relevant to this limitation, Table 2 instructs clinicians that patients who were administered EPA experienced a median 4% reduction in apo B levels from baseline, while patients in the placebo group experienced a median 4% increase in apo B levels

from baseline. Critically, Table 2 further instructs clinicians that administration of icosapent ethyl 4 g per day for 12 weeks caused a median 9% reduction in apo B when compared to placebo control (*i.e.*, compared to the 75 patients who did not receive the treatment). Furthermore, the apo B reduction from baseline relative to placebo was statistically significant. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 427:9–22 (Budoff Direct) ("physicians who are reading the label will be encouraged to reduce apo B. It occurred in the clinical trial section … compared to placebo control, Vascepa will effect a reduction in apolipoprotein B. Q. What was the magnitude of the reduction compared to placebo control in apo B recited in the label? A. Minus 9 percent, and that was statistically significant.").

422. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that EPA 4 g per day reduced both TGs and apo B from baseline relative to placebo in severely hypertriglyceridemic patients. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 427:14–19 (Budoff Direct) ("physicians who are reading the label will be encouraged to reduce apo B. It occurred in the clinical trial section, it's reemphasized in the paragraph below the clinical trial section, that compared to placebo control, Vascepa will effect a reduction in apolipoprotein B.").

423. The Clinical Studies section of Defendants' labeling (and VASCEPA's labeling) thus instructs clinicians that icosapent ethyl 4 g per day reduces apo B compared to placebo control when administered for at least 12 weeks. Clinicians will read this section of Defendants' labeling as encouraging, recommending, promoting, or suggesting that they administer 4 g per day of icosapent ethyl, with the intent and expectation that their severely hypertriglyceridemic patients will experience a reduction in TGs while having the additional beneficial effect of reducing those patients' apo B levels (compared to what they would have been with no treatment). Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered

Defendants' ANDA Products according to the labeling. Trial Tr. 427:2–428:9 (Budoff Direct) (complete discussion of infringement of Claim 8 of the '677 Patent).

424. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a reduction in apolipoprotein B compared to placebo control," as required by Claim 8 of the '677 Patent. Trial Tr. 427:2–428:9 (Budoff Direct).

* * *

425. Clinicians will perform each of the method steps in Claim 8 of the '677 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information. Trial Tr. 428:6–9 (Budoff Direct) ("Q. So will the labeling -- the Vascepa labeling encourage clinicians to follow each step claimed in Claim 8 of the '677 Patent? A. Yes.").

6. Defendants Will Induce Infringement of Claim 14 of the '715 Patent

426. Claim 14 of the '715 Patent is a dependent claim that depends from Claim 13 of the '715 Patent. As a dependent claim, Claim 14 incorporates the limitations in Claim 13.

427. Claim 13 of the '715 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/d[L] to about 1500 mg/d[L], who does not receive a concurrent lipid altering therapy, comprising administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters for a period of at least 12 weeks to effect a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or apolipoprotein B in the subject.

PX 22 ('715 Patent) at 22.

428. Claim 14 of the '715 Patent recites:

> The method of claim 13 comprising administering to the subject about 4 g per day of the pharmaceutical composition to effect a statistically significant reduction in triglycerides and apolipoprotein B without effecting a statistically significant increase of [LDL-C] in the subject.

PX 22 ('715 Patent) at 22.

429. As a dependent claim, Claim 14 of the '715 Patent incorporates the limitations of the claim from which it depends, Claim 13 of the '715 Patent. As discussed above, Defendants will induce direct infringement of the following disputed limitations in Claim 14 of the '715 Patent. Trial Tr. 429:6–12 (Budoff Direct).

"A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"	*See supra* ¶¶ 368–373
"who does not receive concurrent lipid altering therapy"	*See supra* ¶¶ 343–356
"administering orally to the subject"	*See supra* ¶¶ 374–381
"about 4 g per day"	*See supra* ¶¶ 374–381
"of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters"	*See supra* ¶ 365
"for a period of at least 12 weeks"	*See supra* ¶¶ 296–356, 364

Trial Tr. 429:6–12 (Budoff Direct).

430. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe the remaining limitations in Claims 14 of the '715 Patent:

- "to effect a statistically significant reduction in triglycerides and apolipoprotein B"
- "without effect a statistically significant increase of [LDL-C] in the subject"

431. Furthermore, Defendants' proposed labeling, if approved, will induce clinicians to infringe the remaining limitations in Claim 14 of the '715 Patent for the reasons described below.

a) "to effect a statistically significant reduction in triglycerides"

432. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products "to effect a statistically significant

reduction in triglycerides." The same section further conveys to physicians that such a reduction will in fact occur in their patients.

433. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling reports that 4 g per day of EPA effected a 33% reduction in TG compared to placebo in patients with severe hypertriglyceridemia. Notably, Table 2 specifically states that the 33% reduction in TG was statistically significant by reporting a p-value of less than 0.001. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9.

434. Clinicians will read this section of Defendants' labeling as encouraging, recommending, promoting, or suggesting that clinicians administer 4 g per day of icosapent ethyl, with the intent and expectation that those results will in fact be achieved. Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling." Trial Tr. 429:13–432:1 (Budoff Direct).

435. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a statistically significant reduction in triglycerides" as required by Claim 14 of the '715 Patent.

b) "to effect a statistically significant reduction . . . in apo[] B"

436. Defendants' will induce infringement of this limitation because the Clinical Studies section of Defendants' labeling encourages, recommends, promotes, or suggests administration of Defendants' ANDA Products "to effect a statistically significant reduction . . . in apolipoprotein B." The same section further conveys to clinicians that such a reduction will in fact occur in their patients. Trial Tr. 428:12–429:24, 431:2–432:19 (Budoff Direct).

437. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling, like the same table in the Clinical Studies section of VASCEPA's labeling, reports that 4 g per day of icosapent ethyl effected a 9% reduction in apo B compared to placebo. Table 2 further

states that the 9% reduction in apo B was statistically significant by reporting a p-value of less than 0.05. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; *see* Trial Tr. 431:10–20 (Budoff Direct).

438. By instructing clinicians that 4 g per day of icosapent ethyl has been shown to cause a statistically significant reduction in TGs *and* apo B when administered to adult patients with severe hypertriglyceridemia, the Clinical Studies section of Defendants' labeling encourages, recommends, promotes, or suggests that clinicians administer Defendants' ANDA Products with the intent to effect a statistically significant reduction in TGs while having the additional beneficial effect of a statistically significant reduction in apo B. Table 2 further confirms that physicians will observe such a reduction in their patients. Clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling. Trial Tr. 428:12–429:24, 431:2–432:19 (Budoff Direct).

439. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a statistically significant reduction . . . in apolipoprotein B" as required by Claim 14 of the '715 Patent.

c) "without effecting a statistically significant increase of LDL-C"

440. The court previously construed the term "without effecting a statistically significant increase in LDL-C" to mean "without bringing about a rise in LDL-C attributable to the treatment rather than to chance." Claim Construction Order at 9–10 (ECF No. 135).

441. Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to effect a reduction of TGs in a severely hypertriglyceridemic patient without effecting a statistically significant increase in LDL-C—an increase in LDL-C that is attributable to the TG-lowering treatment rather than to chance. Trial Tr. 431:21–432:19 (Budoff Direct).

442. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling, like the same table in the Clinical Studies section of VASCEPA's labeling, reports that patients treated with 4 g per day of EPA experienced a 2% reduction in LDL-C compared to placebo. The Clinical Studies section further states that "[t]he reduction in [triglycerides] observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 431:21-432:1 (Budoff Direct).

443. This LDL-C decrease is not reported as being a statistically significant decrease, but there was also no statistically significant increase. Thus, a statistically significant increase in LDL-C is ruled out. *See* Trial Tr. 431:21–432:1 (Budoff Direct).

444. By communicating to clinicians that EPA reduced LDL-C, Defendants' labels necessarily encourage, recommend, promote, or suggest to clinicians that Defendants' ANDA Products will not raise LDL-C, let alone raise LDL-C by an amount attributable to the treatment rather than to chance. There can be no "rise in LDL-C attributable to the treatment rather than to chance" because there was no rise in LDL-C. Therefore, clinicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling.

445. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—"without effecting a statistically significant reduction in LDL-C" as required by Claim 14 of the '715 Patent. Trial Tr. 432:16–19 (Budoff Direct).

* * *

446. Clinicians will perform each of the method steps in Claim 14 of the '715 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information.

7. Defendants Will Induce Infringement of Claim 4 of the '560 Patent

447. Claim 4 of the '560 Patent is a dependent claim that depends from Claim 1 of the '560 Patent. As a dependent claim, Claim 4 incorporates the limitations in Claim 1.

448. Claim 1 of the '560 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/d[L] to about 1500 mg/d[L] comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject.

PX 30 ('560 Patent) at 22.

449. Claim 4 of the '560 Patent recites:

> The method of claim 1, wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject.

PX 30 ('560 Patent) at 23.

450. As a dependent claim, Claim 4 of the '560 Patent incorporates the limitations of the claim from which it depends, Claim 1 of the '560 Patent.

451. As discussed above, Defendants will induce infringement of the disputed limitations in Claim 4 of the '560 Patent depicted in the following chart, which are the same or similar to the limitations in Claim 1 of the '728 Patent:

"A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl"	*See supra* ¶¶ 368–373
"administering orally to the subject"	*See supra* ¶¶ 374–381
"4 capsules per day"	*See supra* ¶¶ 374–381
"each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present"	Joint Stipulations of Fact ¶ 220 (ECF No. 324) (addressing Defendant Hikma's ANDA Product). Joint Stipulations of Fact ¶¶ 232, 233 (ECF No. 324) (addressing Defendant DRL's ANDA Product).

"for a period of 12 weeks"	*See supra* ¶¶ 296–356, 364

Trial Tr. 433:11–15 (Budoff Direct)

452. Claim 4 of the '560 Patent adds three additional claim limitations not yet addressed:

- "wherein said administering effects a reduction in fasting triglycerides of at least about 10%"
- "without increasing LDL-C by more than 5%"
- "in the subject"

453. Defendants will induce infringement of these limitations because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to "effect[] a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject." This section further conveys to physicians that such effects will in fact occur in patients. Trial Tr. 433:16–435:2 (Budoff Direct).

454. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' proposed labeling, like the same table in VASCEPA's labeling, reports that, when administered for 12 weeks to patients with severe hypertriglyceridemia, EPA 4 g per day caused a median 27% reduction in triglycerides from baseline and a median 33% reduction in triglycerides compared to placebo. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 433:23–434:3 (Budoff Direct).

455. Table 2 in the Clinical Studies section further instructs clinicians that patients treated with 4 g per day of icosapent ethyl experienced a median 5% reduction in LDL-C compared to baseline, as well as a median 2% reduction in LDL-C compared to placebo. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9; Trial Tr. 434:4–6 (Budoff Direct).

456. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that icosapent ethyl 4 g per day "reduced median TG . . . levels from baseline relative to

placebo" and that "[t]he reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9.

457. As explained above, a clinician reading Defendants' labeling (or VASCEPA's labeling) would understand that these lipid measurements were taken in a fasting state. *See supra* ¶ 371.

458. In sum, the Clinical Studies section of Defendants' labeling (and the VASCEPA labeling) instructs clinicians that patients who were administered 4 g per day of icosapent ethyl for 12 weeks experienced reductions in TGs in excess of the minimum "at least 10%" reduction required by Claim 4 of the '560 Patent, and did not experience an increase of LDL-C of more than 5% (but instead saw a reduction in LDL-C compared to baseline and placebo). Trial Tr. 433:16–435:2 (Budoff Direct).

459. Clinicians will read this section of Defendants' labeling (and VASCEPA®'s labeling) as encouraging, recommending, promoting, or suggesting that they administer 4 g per day of icosapent ethyl, with the intent and expectation that Defendants' ANDA Products will reduce severely hypertriglyceridemic patients' TGs by more than "at least 10%" without increasing patients' LDL-C levels by "more than 5%." Trial Tr. 434:1–8 (Budoff Direct). Physicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling. Trial Tr. 434:13–24 (Budoff Direct); Trial Tr. 667:13–20 (Sheinberg Cross).

460. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—to "effect[] a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject" as required by Claim 4 of the '560 Patent. Trial Tr. 433:16–435:2 (Budoff Direct).

* * *

461. Clinicians will perform each of the method steps in Claim 4 of the ’560 Patent, and will be instructed or encouraged to do so by Defendants’ proposed prescribing information. Trial Tr. 434:25–435:2 (Budoff Direct).

8. Defendants Will Induce Infringement of Claim 17 of the ’560 Patent

462. Claim 17 of the ’560 Patent is a dependent claim that depends from Claim 11 of the ’560 Patent. As a dependent claim, Claim 17 incorporates the limitations in Claim 11.

463. Claim 11 of the ’560 Patent recites:

> A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/d[L] to about 1500 mg/d[L] comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject compared to placebo control.

PX 30 (’560 Patent) at 23.

464. Claim 17 of the ’560 Patent recites:

> The method of claim 11, wherein said administering effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control.

PX 30 (’560 Patent) at 23.

465. As a dependent claim, Claim 17 of the ’560 Patent incorporates the limitations of the claim from which it depends, Claim 11 of the ’560 Patent.

466. As discussed above, Defendants will induce infringement of the disputed limitations in Claim 17 of the ’560 Patent depicted in the following chart, which are the same or similar to the limitations in Claim 1 of the ’728 Patent:

“A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl”	*See supra* ¶¶ 368–373
“administering orally to the subject”	*See supra* ¶¶ 374–381
“4 capsules per day”	*See supra* ¶¶ 374–381

"each capsule containing about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present"	Joint Stipulations of Fact ¶ 220 (ECF No. 324) (addressing Defendant Hikma's ANDA Product). Joint Stipulations of Fact ¶¶ 232, 233 (ECF No. 324) (addressing Defendant DRL's ANDA Product).
"for a period of 12 weeks"	*See supra* ¶¶ 296–356, 364

Trial Tr. 435:6–12 (Budoff Direct).

467. Claim 17 of the '560 Patent adds three additional claim limitations not yet addressed.

- "wherein said administering effects a reduction in fasting triglycerides of at least about 20%"
- "without increasing LDL-C in the subject"
- "compared to placebo control"

468. As explained below, Defendants' ANDA Products, and use of Defendants' ANDA Products according to the instructions in Defendants' proposed labeling, if approved, will directly infringe these limitations. For the reasons discussed at ¶¶ 321–337 and 406–413 above, Defendants' proposed labeling will encourage, recommend, promote, and suggest that clinicians administer Defendants' ANDA Products "to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control," as required by Claim 1 of the '677 Patent, and conveys that such effects will in fact occur in patients with severe hypertriglyceridemia. Trial Tr. 435:13–436:3 (Budoff Direct).

469. These limitations differ from that in Claim 1 of the '677 Patent only in the magnitude of the lipid effects disclosed. Whereas Claim 1 of the '677 Patent required a reduction in TGs, this claim—Claim 17 of the '560 Patent—requires a reduction in TGs of at least 20%. And whereas Claim 1 of the '677 Patent required the reduction in TGs without *substantially increasing* LDL-C, this claim requires that TGs be reduced (by at least 20%) without *increasing* LDL-C.

470. Defendants will induce infringement of these limitations because clinicians will read the Clinical Studies section of Defendants' labels, like the Clinical Studies section of the VASCEPA label, as encouraging, promoting, recommending, or suggesting administration of Defendants' ANDA Products to "effect[] a reduction in fasting triglycerides of at least 20% without increasing LDL-C in the subject compared to placebo control." The Clinical Studies section further conveys to physicians that such effects will in fact occur in their patients. Trial Tr. 435:20–436:20 (Budoff Direct).

471. ***Clinical Studies Section.*** Table 2 in the Clinical Studies section of Defendants' labeling instructs clinicians that 4 g per day of icosapent ethyl, when administered to severely hypertriglyceridemic patients for 12 weeks, effected a median 33% reduction in TGs compared to placebo and a median 2% reduction in LDL-C compared to placebo. PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9.

472. Beneath Table 2, the Clinical Studies section also specifically highlights for clinicians that "[i]cosapent ethyl 4 grams per day reduced median TG . . . levels from baseline relative to placebo," and that "[t]he reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." PX 1186 (VASCEPA Label 2019) at 11; PX 1203 (Hikma 2019 Proposed Label) at 7–8; PX 1209 (DRL 2020 Proposed Label) at 8–9.

473. As explained above, a clinician reading Defendants' labeling (or VASCEPA's labeling) would understand that these lipid measurements were taken in a fasting state. *See supra* ¶¶ 371.

474. The Clinical Studies section of Defendants' labeling thus instructs clinicians administering 4 g per day of EPA for at least 12 weeks, they can expect to reduce most patients' fasting TG levels by more than "at least 20%" without increasing LDL-C compared to placebo, as required by Claim 17 of the '560 Patent.

475. Clinicians will read this section of Defendants' labeling (and VASCEPA's labeling) as encouraging, recommending, promoting, or suggesting that clinicians administer 4 g per day of EPA, with the intent and expectation that Defendants' ANDA Products will reduce severely hypertriglyceridemic patients' fasting TG levels by at least 20% without increasing LDL-C compared to placebo. Physicians respond to the instructions in Defendants' labeling by administering Defendants' ANDA Products according to that labeling, and the claimed results are in fact achieved in patients administered Defendants' ANDA Products according to the labeling. Trial Tr. 435:6–436:20 (Budoff Direct). Indeed when clinicians administer Vascepa they typically see a greater than 20% reduction in TGs.

476. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—to "effect[]reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control," as required by Claim 17 of the '560 Patent. Trial Tr. 435:6–436:20 (Budoff Direct).

* * *

477. Clinicians will perform each of the method steps in Claim 17 of the '560 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information. Trial Tr. 436:17–20 (Budoff Direct).

9. Defendants Will Induce Infringement of Claim 1 of the '929 Patent

478. Claim 1 of the '929 Patent is an independent claim.

479. Claim 1 of the '929 Patent recites:

> A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/d[L] comprising, orally administering to the subject daily for at least about 12 weeks a pharmaceutical composition comprising about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids.

PX 31 ('929 Patent) at 22–23.

480. As discussed above, Defendants will induce infringement of the disputed limitations in Claim 1 of the '929 Patent depicted in the following chart, which are the same or similar to the limitations in Claim 1 of the '728 Patent:.

"A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of at least 500 mg/dl"	*See supra* ¶¶ 368–373
"orally administering to the subject"	*See supra* ¶¶ 374–381
"daily for at least about 12 weeks"	*See supra* ¶¶ 296–356, 364
"a pharmaceutical composition comprising composition about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids"	*See supra* ¶ 365

Trial Tr. 437:8–10 (Budoff Direct).

481. The first limitation differs from, for example, the limitation in Claim 1 of the '728 Patent, because it requires that the subject have "fasting triglycerides of at least 500 mg/dl," rather than "a fasting baseline triglyceride level of 500 mg/dl *to about 1500* mg/dl."

482. The parties agree that the term "at least 500 mg/dl" is construed to mean "500 mg/dl and above." *See* Construction of Claim Terms On Which Parties Agree at 4 (ECF No. 83–2).

483. Thus, for the reasons explained in *supra* ¶¶ 368–373, Defendants will induce infringement of this limitation because clinicians will read the Indications and Usage and Clinical Studies sections of Defendants' labels as encouraging, recommending, promoting, or suggesting the use of Defendants' ANDA Products in "[a] method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl." Trial Tr. 436:21–437:20 (Budoff Direct).

484. Otherwise, all of the limitations in this Claim are similar to limitations already addressed.

485. Clinicians will perform each of the method steps in Claim 1 of the ’929 Patent, and will be instructed or encouraged to do so by Defendants’ proposed prescribing information. Trial Tr. 437:17–20 (Budoff Direct).

10. Defendants Will Induce Infringement of Claim 5 of the ’929 Patent

486. Claim 5 of the ’929 Patent is dependent upon Claim 1 of the ’929 Patent. As a dependent claim, Claim 5 incorporates the limitations in Claim 1, addressed above.

487. Claim 5 of the ’929 Patent recites:

> The method of claim 1, wherein 12 weeks of said daily administration is effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dL.

PX 31 (’929 Patent) at 23.

488. Claim 5 adds one additional limitation:

- “effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dl”

489. Defendants’ ANDA Products, and use of Defendants’ ANDA Products according to the instructions in Defendants’ proposed labeling, if approved, will directly infringe the remaining limitations in Claim 5 of the ’929 Patent. Furthermore, Defendants’ proposed labeling, if approved, will induce clinicians to infringe the remaining limitations in Claim 5 of the ’929 Patent for the reasons described below. Trial Tr. 438:4–12 (Budoff Direct).

490. For these reasons, based on the instructions in Defendants’ proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—for “12 weeks of said daily administration,” as required by Claim 5 of the ’929 Patent.

491. The claim limitation, “effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dl” contains similar language to other claims previously addressed.

492. For the reasons discussed at ¶ 368 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products to patients "who have fasting triglycerides levels of at least 500 mg/dL."

493. For the reasons discussed at ¶¶ 388–342 and 436–439 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products to effect a statistically significant reduction in apo B in patients with fasting baseline TG levels between 500 mg/dL and 1500 mg/dL. Trial Tr. 438:4-439:1 (Budoff Direct).

494. For the reasons discussed at ¶¶ 414–425 above, Defendants' proposed labeling will induce clinicians to administer Defendants' ANDA Products to effect a reduction in apo B compared to placebo control in patients with fasting baseline TG levels between 500 mg/dL and 1500 mg/dL. Trial Tr. 438:4-439:15 (Budoff Direct).

495. For these same reasons, Defendants will induce infringement of this limitation because clinicians will read the Clinical Studies sections of Defendants' labeling as encouraging, recommending, promoting or suggesting administration of Defendants' ANDA products to "effect[]" a "reduc[tion]" in "apolipoprotein B" in patients with fasting baseline TG levels of at least 500 mg/dL." Trial Tr. 437:21–439:15 (Budoff Direct).

496. Clinicians will perform each of the method steps in Claim 5 of the '929 Patent, and will be instructed or encouraged to do so by Defendants' proposed prescribing information. Trial Tr. 439:8–15 (Budoff Direct).

XII. DEFENDANTS HAVE FAILED TO PROVE CLEARLY AND CONVINCINGLY THAT THE ASSERTED CLAIMS ARE INVALID AS OBVIOUS

A. Introduction

497. The sole invalidity defense maintained by Defendants at trial was that the Asserted Claims are invalid as obvious under 35 U.S.C. § 103. Defendants have conceded that they are not asserting anticipation under 35 U.S.C. § 102—and hence do not dispute that the Asserted Claims are novel over the prior art. *See* Order on Summary Judgment, ECF No. 278 at 16, 24; *Defendants' Opposition to Amarin's Motion for Partial Summary Judgment* (ECF No. 247) at 1. Defendants

have also conceded that they are not asserting that the Asserted Claims are invalid under 35 U.S.C. § 112 as indefinite or lacking enablement. *See id.* Additionally, this Court previously held that Defendants failed to preserve the defense of lack of written description. *See* Order on Summary Judgment, ECF No. 278 at 16–19, 24.

498. Defendants' obviousness defense rests upon four prior art references that they call their "key prior art": (1) Lovaza PDR (DX 1535); (2) Mori 2000 (DX 1538); (3) Hayashi (DX 1532); and (4) Kurabayashi (DX 1534). *See* Trial Tr. at 718:20–719:3 (Heinecke Direct); *see also id.* at 828:10–22 (Heinecke Cross).

499. Lovaza PDR, the 2007 prescribing information for Lovaza, described the use of a mixture of omega-3 fatty acid esters, including both EPA and DHA, to reduce TGs in patients with severe hypertriglyceridemia. *See generally* DX 1535 (Lovaza PDR) at 2–3. As this prescribing information noted, however, Lovaza's reduction in TGs was accompanied by a large increase in LDL-C, and the Lovaza PDR thus warned that a patient's LDL-C levels should be monitored during therapy. *See id.* at 2–3. Defendants contend that their other "key" prior art taught that it was DHA, but not EPA, that was responsible for Lovaza's increase in LDL-C, and that this other prior art would have motivated a person of ordinary skill in March 2008 to use a formulation with highly purified EPA (and substantially no DHA) to treat severe hypertriglyceridemia to avoid this rise in LDL-C, with a reasonable expectation of success of avoiding such LDL-C increases. Trial Tr. at 759:10–760:1 (Heinecke Direct); *see also id.* at 828:23–829:22 (Heinecke Cross).

500. Defendants' burden to prove obviousness is a heavy one. An issued patent is presumed valid, and Defendants bear the burden of proving obviousness to a clear and convincing standard. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Moreover, in this case, all of Defendants' "key" prior art, and a considerable part of all of the art they cite, was considered by the Patent Examiner during prosecution of the asserted patents—making Defendants' validity challenge even more difficult. PX 21 ('728 Patent) at 3–13; *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("[I]t may be harder to meet the clear and convincing burden

when the invalidity contention is based upon the same argument or the same reference that the PTO already considered.").

501. Defendants' validity challenge is especially difficult here. The Notice of Allowance makes clear that the Patent Office allowed the Asserted Claims based on evaluation of the objective indicia of non-obviousness—an important (indeed, mandatory) safeguard against impermissible hindsight. PX 380 (Notice of Allowance) at 8-13; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). The evidence supporting the objective indicia has only gotten stronger—since the Patent Office granted the Asserted Patents, the VASCEPA invention has demonstrated the dramatic and unexpected benefit of reducing cardiovascular risk in patients with severe hypertriglyceridemia, as demonstrated by the REDUCE-IT trial—thereby meeting another long-felt need, demonstrating more unexpected results, and garnering more praise. *See infra* ¶¶ 797–806. It is undisputed that VASCEPA is the first, and remains the only, drug to show cardiovascular benefit in severely hypertriglyceridemic patients. Trial Tr. 15–21 (Heinecke Cross); *id*. at 1122:6–14 (Fisher Cross).

502. Moreover, Defendants' assertion that the prior art rendered it obvious that purified EPA could be used to lower TGs in patients with severe hypertriglyceridemia without raising LDL-C is contradicted by the actual course of events. As Defendants acknowledge, a purified EPA product, Epadel, had been used in Japan to treat hyperlipidemia since at least 1991 (Trial Tr. 719:9–25 (Heinecke Direct)), and the prior art had expressed "major clinical concern" about large LDL-C increases with severe hypertriglyceridemia treatments well before that. DX 1026 (Carlson) at 7. Additionally, it had been shown in clinical trials by the mid-1990s (at the latest) that omega-3 fatty acids dramatically increased LDL-C in patients with severe hypertriglyceridemia. DX 1531 (Harris) at 1.

503. Despite these clear teachings, two sophisticated drug companies, Reliant and GSK, moved forward with the development of Lovaza® for the treatment of severe hypertriglyceridemia. Trial Tr. 889:1–890:1 (Heinecke Cross). Lovaza was first approved in the

United States in 2004, Trial Tr. 952:15-20 (Fisher Direct)—well after all of the "key" prior art Defendants contend rendered it obvious that purified EPA would avoid the LDL-C increases with Lovaza. Hadthe prior art rendered it obvious that purified EPA had advantages over the Lovaza mixture, GSK and Reliant would have developed a purified EPA product for severe hypertriglyceridemia. To the contrary, as Dr. Fisher acknowledged, at the time no one suggested removing the DHA from Lovaza and no conclusions were drawn from the literature about the clinical superiority of either EPA or DHA. Trial Tr. 1187:4–25 (Fisher Cross). This real world evidence makes manifest that it was NOT obvious to use purified EPA to treat severe hypertriglyceridemia; it surely refutes Defendants' assertion that the prior art clearly and convincingly made it obvious to do so.

504. The prevailing view at the time of the invention was that the increase in LDL-C seen in patients with severe hypertriglyceridemia was a direct consequence of reducing TGs in those patients—specifically, that the enhanced conversion of the TG-rich VLDL particles to LDL particles necessarily resulted in a large rise in LDL-C. *See supra* ¶¶ 39–53; *infra* ¶¶ 704–19. The prior art expressly taught that both DHA and EPA, "like fibrates," reduced TGs in precisely this manner, leading a person of ordinary skill in March 2008 to expect that purified EPA—like every other TG-lowering drug approved up to that time to treat severe hypertriglyceridemia—would increase LDL-C in patients with severe hypertriglyceridemia. *See* PX 923 (McKenney) at 5; PX 486 (Bays 2008) at 10,12; Trial Tr. 1589:10–1598:17 (Toth Direct); *see also supra* ¶¶ 39–53.

505. Defendants' assertion that the prior art showed that EPA did not raise LDL-C in other patients, with lower TG levels, fails to support obviousness for at least two reasons.

506. *First*, Defendants are simply wrong that the prior art clearly taught that EPA did not raise LDL-C—in any type of patient with elevated TG levels. Mori 2000—which did not even study patients with severe hypertriglyceridemia, but instead itself showed a 3.5% *rise* with EPA. DX 1538 (Mori 2000) at 3; Trial Tr. 1642:14–1643:2 (Toth Direct). While the increase was not statistically significant, a person of ordinary skill would have attributed the lack of statistical significance to Mori's small sample size—particularly in light of the fact that other studies with

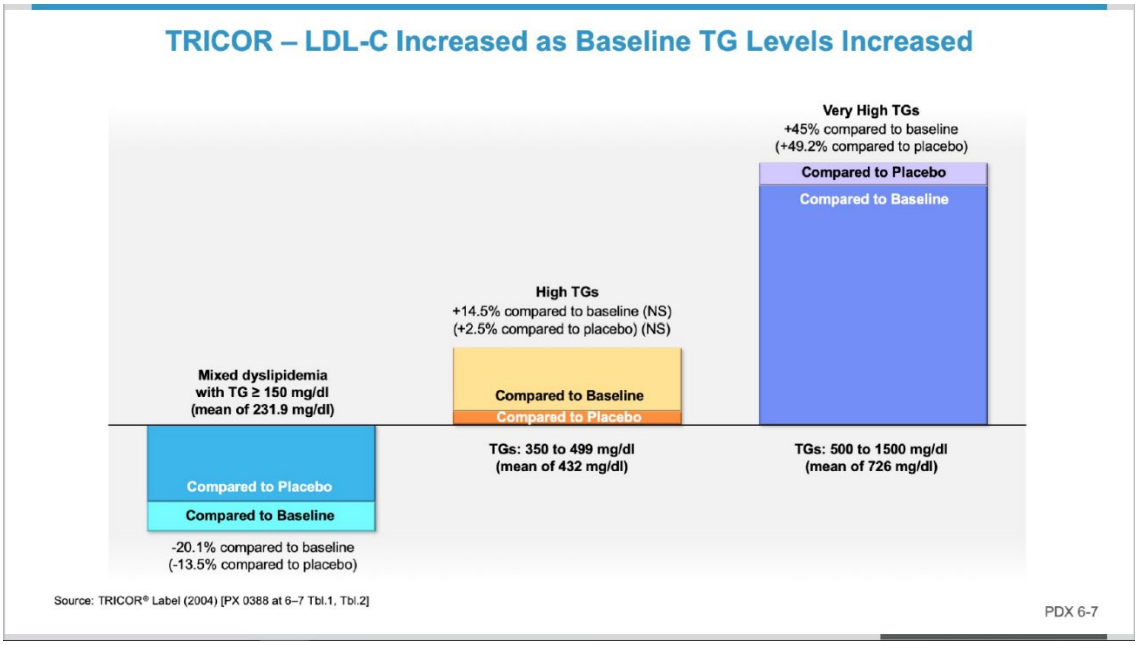
EPA in larger samples had shown a statistically significant increase in LDL-C. *See* DX 1961 (Rambjør) at 3, 5, Tbl. 3; Trial Tr. 1643:20–1644:11, 1692:7-25 (Toth Direct). The prior art therefore did not demonstrate, clearly and convincingly, that EPA would not raise LDL-C—even in patients with TGs below 500 mg/dL.

507. A review of the literature as a whole reached the conclusion that *both* DHA and EPA raised LDL-C, even in patients with TGs below 500 mg/dL—refuting Defendants' assertion that the literature clearly taught that EPA avoided any such increase. DX 1605 (von Schacky) at 9, Tbl. 1; Trial Tr. 1698:2–1699:24 (Toth Direct). Defendants' own expert, Dr. Fisher, conceded that the literature was "back and forth" on the differential effects of DHA and EPA—and that he was aware of no one suggesting that the DHA should be removed from Lovaza. Trial Tr. 1187:3–25 (Fisher Cross).

508. *Second*, even were Defendants correct that purified EPA had been shown not to raise LDL-C in patients with TG levels lower than 500 mg/dL, that still would not have rendered obvious high purity EPA's use in patients with severe hypertriglyceridemia, or created a reasonable expectation that EPA would avoid substantial LDL-C increases in that population. None of Defendants' prior art describes EPA's effects on LDL-C in patients with severe hypertriglyceridemia. *See* Trial Tr. 800:2–5 (Heinecke Direct) ("And so I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter."); *see also* Trial Tr. 798: 23–799:11 (Heinecke Direct) ("I'm not arguing here that we know what the impact is of EPA on LDL cholesterol levels above 500 milligrams per deciliter"); Trial Tr. 1667:11–19 (Toth Direct). And a person of ordinary skill at the time of the invention would have strongly expected that EPA would dramatically increase LDL-C in patients with severe hypertriglyceridemia.

509. Patients with severe hypertriglyceridemia were known to be particularly subject to large increases in LDL-C as a consequence of treatments that lowered TGs. Trial Tr. 1574:1–1598:17 (Toth Direct). Administration of other TG-lowering agents with similar mechanisms of action, such as fibrates, dramatically increased LDL-C in severely hypertriglyceridemic patients,

despite reducing LDL-C along with TGs in other patients with moderately elevated TG levels (TG levels of 231.9 mg/dL), including those with mixed dyslipidemia, like the patients studied in Mori 2000. Trial Tr. 1579:6–1584:19, 1590:12–1598:17 (Toth Direct); PX 388 (Tricor label) at 6, 7; Tbls. 1–2; *see also* PX 1027 (Goodman & Gilman 2006) at 31; PDX 6-7.



510. The population studied in Mori 2000 had mixed dyslipidemia, with moderately elevated TGs and LDL-C. Trial Tr. 830:18–831:3 (Heinecke Cross). In that regard, they are most similar to the the mixed dyslipidemic population in the Tricor prescribing information, who experienced a decrease in LDL-C (and TGs) when administered Tricor. PX 388 (2004 Tricor Label) at 6 Tbl. 1; Trial Tr. 1667:20–1669:16 (Toth Direct). A person of ordinary skill in March 2008 thus would have understood that even an agent that lowered LDL-C—let alone one like EPA that showed in Mori 2000 a small, non-significant increase in LDL-C—could nonetheless be expected to increase LDL-C dramatically in severely hypertriglyceridemic patients. At a minimum, a POSA could not reasonably expect to avoid such an increase. Trial Tr. 1574:1–1598:17, 1665:17–1669:16 (Toth Direct).

B. Obviousness Legal Standard

1. Obviousness Standard

511. Under 35 U.S.C. § 103, a patent is invalid as obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." Whether a patent claim is obvious is a question of law based on four underlying factual determinations: (1) "the scope and content of the prior art"; (2) "the level of ordinary skill in the pertinent art"; (3) the "differences between the prior art and the claims at issue"; and (4) "[s]uch secondary considerations as commercial success, long-felt but unsolved needs, [and the] failure of others . . . ." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966).

512. "A party seeking to invalidate a patent based on obviousness must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). Defendants, as the accused infringers, bear the ultimate burden of proving, by clear and convincing evidence, that the Asserted Claims are invalid. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011).

513. The determination of obviousness must be based on the knowledge clearly possessed by one of ordinary skill in the art at the time the invention was made. It is not permissible to use hindsight after viewing the inventor's own path to determine questions of obviousness or to rely on the teachings of the claimed invention in determining whether one of ordinary skill in the art would have found the invention obvious. "The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Millennium Pharm.*,

Inc. v. Sandoz Inc., 862 F.3d 1356, 1367 (Fed. Cir. 2017) (quoting *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012)).

2. Obvious to Try

514. An invention may be "obvious to try" only if there are "a finite number of identified, predictable solutions" that lead to "anticipated success." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). "To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identifiable, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

515. Moreover, "[e]vidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012) (quoting *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

3. Objective Indicia of Non-Obviousness

516. The obviousness inquiry must consider whether objective indicia of non-obviousness support the Asserted Claims. "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17–18; *see also In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (explaining that objective evidence of nonobviousness may include copying, long-felt but unsolved need, failure of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans).

517. "Objective indicia of nonobviousness play a critical role in the obviousness analysis. They are 'not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness.'" *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quoting *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008)). Objective indicia of non-obviousness, "when considered with the balance of the obviousness in the record, guard against hindsight bias." *Cyclobenzaprine*, 676 F.3d at 1079 (citing *Graham*, 383 U.S. at 36).

518. "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Indeed, "[i]t is the secondary considerations that are often the most probative and determinative of the ultimate conclusion of obviousness or nonobviousness." *Pro-Mold & Tool Co., Inc. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996).

519. "There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity." *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

520. "[P]atentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest." *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014). Moreover, "reliance on an unexpected property not disclosed in the application may be entitled to weight if 'directed to that which would inherently flow from what was originally disclosed.'" *Id*. (quoting *In re Khelghatian*, 53 CCPA 1441, 364 F.2d 870, 876 (1966)); *see also Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 769 F.3d 1339, 1343 (Fed. Cir. 2014) (O'Malley, J., concurring in denial of *en banc* rehearing) ("Indeed, as we have said repeatedly over the years, post-issuance evidence regarding

objective indicia of non-obviousness may often be the most probative and cogent evidence in the record. This is especially true where the post-issuance evidence relates to unexpected results.") (internal citations omitted).

521. There must be a nexus between the merits of the claimed invention and the objective indicia of non-obviousness. "[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) (internal quotations omitted).

522. "Evidence of secondary considerations must be reasonably commensurate with the scope of the claims. This does not mean that an applicant is required to test every embodiment within the scope of his or her claims. If an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with scope of the claims." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (internal citations omitted).

C. Definition of a Person of Ordinary Skill in the Art

523. The Asserted Claims and the prior art are evaluated at the time of the invention from the standpoint of a person of ordinary skill in the art. A person of ordinary skill in the art is a hypothetical person who is presumed to have access to, and be aware of, all of the relevant prior art at the time of the invention. Factors that may be considered in determining the level of ordinary skill in the art may include: (1) type of problems encountered in the art, (2) prior art solutions to those problems, (3) rapidity with which innovations are made, (4) sophistication of the technology, and (5) educational level of active workers in the field. *See Envtl. Designs, Ltd. v. Union Oil Co. of California*, 713 F.2d 693, 696 (Fed. Cir. 1983).

524. The person of ordinary skill in the art in this case would be (1) a clinician with an M.D., or D.O. and at least 2 to 3 years of experience in the diagnosis, evaluation, and treatment of lipid blood disorders, including severe hypertriglyceridemia (*i.e.*, TG levels of at least 500 mg/dL),

or (2), alternatively, a clinician, such as a nurse practitioner or physician's assistant, with 3 to 5 years of experience in the diagnosis, evaluation, and treatment of lipid blood disorders, including severe hypertriglyceridemia. Trial Tr. 1637:3–18 (Toth Direct). While Defendants proposed a different definition for the person of ordinary skill in the art, *see* Trial Tr. 717:20–718:6 (Heinecke Direct), both sides agree that the infringement and validity analyses remain the same regardless of which definition is used. Trial Tr. 718:7–13 (Heinecke Direct); Trial Tr. 1637:19–1638:1 (Toth Direct).

D. Priority Date

525. The Asserted Patents are entitled to a priority date of no later than March 2008. That is the date supported by inventor testimony. *See, e.g.*, Manku Dep. Tr. 131:15–132:17. Both side's experts used that date in formulating their opinions, and Defendants' experts have not challenged it. *See, e.g.*, Trial Tr. 714:17–21 (Heinecke Direct); Trial Tr. 1638:2–4 (Toth Direct) ("Q: And in evaluating whether the claims were obvious, are you using the same March 2008 date that Dr. Heinecke did? A: Yes.").

526. The undisputed record demonstrates that (1) the invention was conceived by early 2008 through oral testimony of the inventor; (2) written corroboration supports the inventor's testimony; and (3) the inventors exercised reasonable diligence in reducing the invention to practice. *See Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996) ("Priority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive the invention and that it exercised reasonable diligence in later reducing that invention to practice.") (internal quotations omitted).

527. As of March 2008, Dr. Manku—one of the named inventors on the Asserted Patents—had obtained extensive data on the blood plasma effects of purified EPA from neuropsychiatric clinical program sponsored by Amarin and its predecessor, Laxdale Ltd. Manku Tr. 32:20–33:16; 35:2–6. Among other things, this provided Dr. Manku with the metabolism and function of EPA and the "blood chemistry" and "biochemical effect" of 2 and 4 grams of EPA per day. *Id.* at 79:21–80:25. By March 2008, Dr. Manku obtained the clinical results from a Laxdale-

sponsored study of purified EPA in schizophrenic patients—whose drug treatment subjected them to large increases in TGs—and observed that EPA reduced TGs in these patients without raising their LDL-C. *See supra* ¶¶ 59–67; *see also* DX 1857 (Mar. 25, 2008 M. Manku E-mail) at 1; Manku Dep. 162:5–164:16 (testifying about DX 1857). Based on his extensive experience studying fatty acids, including EPA, Dr. Manku believed that EPA would not raise LDL-C, in contrast to all prior approved medications for severe hypertriglyceridemia. *See supra* ¶¶ 59–67. And during this time, by early 2008, Dr. Manku was also educating his colleagues on his belief that EPA would work differently from prior medications in severely hypertriglyceridemic patients. *See supra* ¶¶ 59–67; *see also* Manku Dep. 140:7–141:24 ("I was trying to convince my colleagues: Look, this is . . . going to be a different type of mechanism.").

528. At that point, Dr. Manku then worked with his co-inventors to pursue an indication for purified EPA for the treatment of severe hypertriglyceridemia, including by designing a clinical program to prove that purified EPA was effective and should be approved to treat severe hypertriglyceridemia. *See, e.g.*, PX 755 (Mar. 10, 2008 Osterloh E-mail) at 3 (explaining the rationale for and contemplated components of Amarin's severe hypertriglyceridemia clinical program); Osterloh Dep. Tr. 119:3–121:8 (testifying regarding same); DX 1886 (Jan. 23, 2008 I. Osterloh E-mail) at 1 (conferring with co-inventor, Dr. Pierre Wicker, regarding design of clinical studies to support the development of EPA for severe hypertriglyceridemia); Osterloh Dep. 138:16–22, 139:20–22, 139:24–140:6, 140:8–10, 140:12–141:11 (testifying about DX 1886 and explaining that in early 2008, the inventors were preparing to consult with experts "on the design and conduct of the clinical trial program"). These emails corroborate Dr. Manku's testimony that Amarin and the inventors had conceived of the inventions described in the Asserted Claims by March 2008. *See, e.g.*, Manku Dep. 131:15–19, 132:1–2, 132:4, 132:6–17.

529. Thereafter, Amarin pursued a two-part clinical program to support FDA approval of a purified EPA pharmaceutical product. To that end, beginning in May 2008, Amarin proposed a clinical program (the MARINE trial) to prove the effectiveness of 4 grams per day of EPA in treating severe hypertriglyceridemia, along with a second clinical program (ANCHOR) to show

EPA's favorable action on biomarkers of CV risk in mixed dyslipidemia. *See supra* ¶¶ 68–79; *see also* PX 482 (May 9, 2008 Ltr. From Amarin to FDA Requesting Pre-IND Meeting (Pre-IND FDA Meeting Request)) at 4, ¶¶ 9–10; Trial Tr. 72:14–74:11 (Ketchum Direct). Therefore, the inventors exercised reasonable diligence in constructively reducing the invention to practice in the February 2009 Provisional Application. *See Frazer v. Schlegel*, 498 F.3d 1283, 1288 (Fed. Cir. 2007) ("The filing of a patent application is a constructive reduction to practice of the invention disclosed therein.") (citing *Hyatt v. Boone*, 146 F.3d 1348, 1352 (Fed. Cir. 1998)).

530. The parties agree that the obviousness analysis would not change if February 2009 were used as the priority date rather than March 2008. *See* Trial Tr. 827:8–10 (Heinecke Direct) ("Q: Would your opinions with respect to obviousness change if you were analyzing the obviousness as of February 2009? A: No."); Trial Tr. 1638:5–10 (Toth Direct) ("Q: Do you recall that Dr. Heinecke testified that his opinions would not be different if he used the date of February 2009? A: Yes. Q: Would your opinions also remain the same? A: Yes.").

E. Prosecution

531. As discussed above, the U.S. Applications that ultimately issued as the Asserted Patents are continuations of U.S. Application No. 12/702,889, filed on February 9, 2010, which ultimately issued as U.S. Patent No. 8,293,727 ('727 Patent). *See supra* ¶¶ 94–95; *see also* Joint Stipulations of Fact ¶ 10 (ECF No. 324). The Asserted Patents further claim priority to U.S. Provisional Application No. 61/151,291, filed on February 10, 2009, and U.S. Provisional Application No. 61/173,755, filed on April 29, 2009. *See supra* ¶ 95; *see also* Joint Stipulations of Fact ¶ 11 (ECF No. 324).

532. During the prosecution of the Asserted Patents, Defendants' "key prior art"—as well as numerous other prior art references—were considered by the Patent Examiner. *See* PX 21 ('728 Patent) at 2–13. In addition, Amarin submitted several declarations, from multiple experts including Dr. Harold Bays and Dr. Howard Weintraub, in support of patentability. *See, e.g.*, PX 38 ('727 Patent File History) at 129–31 (Bays I Declaration), 170–72 (Weintraub I Declaration),

976–84 (Weintraub II Declaration), 1211–26 (Bays II Declaration), 1710–18 (Bays III Declaration).

533. In the Bays I Declaration, Dr. Bays submitted and discussed the results of the MARINE Clinical Study, and expressed his surprise that AMR101 reduced TGs in severely hypertriglyceridemic patients without causing a statistically significant increase in LDL-C. PX 38 ('727 Patent File History) at 130 (Bays I Declaration ¶¶ 12–13), 140–48 (attaching the results of the MARINE Clinical Study). Dr. Bays expressed his opinion that the absence of a substantial rise in LDL-C met a long-felt but unmet medical need for a therapy that would lower TGs in this class of patients. *See* PX 38 ('727 Patent File History) at 130–31 (Bays I Declaration ¶¶ 8–13, 17). Like Dr. Bays, Dr. Weintraub noted that for prior treatments, the dramatic rise in LDL-C associated with treating triglycerides in severe hypertriglyceridemia patients was not observed in patients with lower TG levels. *See id.* at 171 (Weintraub I Declaration ¶¶ 8–13); *see also id.* at 982–83 (Weintraub II Declaration ¶¶ 33–35). Dr. Weintraub, in his second declaration, analyzed the available data and concluded that Lovaza and Epadel had a similar impact on both TGs and LDL-C in the subjects with borderline high/high TGs. *See id.* at 983 (Weintraub II Declaration ¶ 37).

534. In the Bays II Declaration, Dr. Bays reiterated his opinion that it was unexpected that VASCEPA would avoid an increase in LDL-C in severe hypertriglyceridemia patients. *See id*. at 1224 (Bays II Declaration ¶¶ 55–56) ("[I]t was my opinion that a person trained in endocrinology and lipid disorders would not have had any basis (other than hope) for concluding that no statistical rise in LDL-C would have occurred in the MARINE study . . . ."). He also expressed his opinion regarding "the unexpected and unique nature of [VASCEPA's] reduction in [apo B]." *Id*. at 1214 (Bays II Declaration ¶¶ 13–15).

535. And in his third declaration, Dr. Bays reiterated the unexpected finding that VASCEPA reduced apo B levels in the MARINE trial. He explained that in view of the Lovaza data, it would not have been expected that 4 g per day of AMR101 [VASCEPA] would significantly reduce apo B levels in severe hypertriglyceridemia patients. *See id.* at 1713–14 (Bays III Declaration ¶¶ 14–17).

536. Amarin also submitted two declarations by Dr. Philip Lavin, a biostatistician. *See, e.g.*, PX 38 ('727 Patent File History) at 1233–37 (Lavin I Declaration), 1725–29 (Lavin II Declaration).In those declarations, Dr. Lavin evaluated conclusions drawn by the Patent Examiner about three pieces of prior art. *See, e.g.*, *id*. at 1233–37 (Lavin I Declaration), 1725–29 (Lavin II Declaration). Specifically, these declarations addressed the statistical likelihood that subjects with certain baseline TG levels were included in the studies disclosed in the prior art references. *See, e.g.*, *id*. 1233–37 (Lavin I Declaration), 1725–29 (Lavin II Declaration).

537. When allowing the claims of the '727 Patent, the Patent Examiner included a detailed Statement of Reasons for Allowance in accordance with 37 C.F.R. § 1.104(e) and the specific guidance set forth in section 1302.14 of the Manual of Patent Examination Procedure. *See supra* ¶¶ 96–108; *see also* PX 38 ('727 Patent File History) at 1829–35. In granting the '727 Patent, the Examiner relied on objective indicia of non-obviousness—in particular, a showing that the applicants demonstrated unexpected results (an unexpected reduction in apo B), and satisfied a long-felt unmet medical need through their invention of a method of treatment that lowered TGs in persons with severe hypertriglyceridemia without substantially increasing LDL-C, as prior treatments had done. *Id*. at 1831–34. The Examiner did not rely on the Lavin Declarations in the Statement of Reasons for Allowance, *see id.*, and the subject of the Lavin Declarations is unrelated to objective indicia, the basis on which the Examiner granted the patents, *see id.* at 1233–37 (Lavin I Declaration), 1725–29 (Lavin II Declaration); *see also* Trial Tr. 908:17–20 (Heinecke Cross).

538. As discussed above, 37 C.F.R. § 1.104(e) provides that "[i]f the examiner believes that the record of the prosecution as a whole does not make clear his or her reasons for allowing a claim or claims, the examiner may set forth such reasoning." Accordingly, as authorized by 37 C.F.R. § 1.104(e), the Examiner made the prosecution history record clear by discussing the specific reasons why the claims were patentable in the Reasons for Allowance. *See supra* ¶¶ 96–108; *see also* PX 38 ('727 Patent File History) at 1829–35 (Notice of Allowance).

539. After discussing the scope of the claims, the Examiner found that the claims were not anticipated but concluded that they were "prima facie" obvious. *See, e.g.*, PX 38 ('727 Patent

File History) at 1830. Nonetheless, the Examiner found the pending claims patentable because "Applicant was able to overcome the above 103 obviousness rejection by showing: 1 - Unexpected results, and 2 - Long felt unmet medical need." *See, e.g.*, PX 38 ('727 Patent File History) at 1831 (Notice of Allowance). The Examiner then discussed evidence of objective indicia supporting the ultimate conclusion that the claims were patentable. *See, e.g.*, *id* at 1831–34.

540. In these pages, the Examiner discussed at length the September 11, 2011 Weintraub and May 16, 2012 Bays declarations and how they evidenced the objective indicia of unexpected results and long-felt unmet medical need that overcame the Examiner's *prima facie* obviousness rejection. *See, e.g.*, *id.* These are the only declarations discussed in the Examiner's Reasons for Allowance. *See, e.g.*, *id.*

541. The Examiner's Statement of Reasons for Allowance reflects the type of record clarification contemplated by MPEP § 1302.14(II)(A) by inclusion of an Examiner's statement of reasons for allowance: when "claims are allowed on the basis of one (or some) of *a number of arguments and/or affidavits* presented, and a statement is necessary to identify which of these arguments and evidence were found to be most persuasive." *See* Trial Tr. 908:4–16 (Heinecke Cross).

542. The Examiner's Statement of Reasons for Allowance thus tracks MPEP § 1302.14 by identifying which affidavits of the multiple affidavits that were submitted support the Examiner's allowance of the claims. PX 38 ('727 Patent File History) at 1831–34 (Notice of Allowance). The Examiner expressly stated that the September 11, 2011 Weintraub and May 16, 2012 Bays declarations provided the basis for overcoming the prima showing of obviousness by establishing both unexpected results and long felt unmet need in the prior art. *Id.* Other declarations in the prosecution history therefore did not serve as the basis for the Examiner's reasons for allowance of the claims.

543. Although the Examiner was correct in allowing the Asserted Claims, the Examiner incorrectly concluded that the Asserted Claims were *prima facie* obvious. *See infra* § XII.F–X. Regardless of the Examiner's reasoning, however, the burden of proof is the same: clear and

convincing evidence of invalidity. *See, e.g.*, *Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 99–102 (2011).

544. Though Dr. Heinecke offered opinions on the prosecution of the Asserted Patents—specifically regarding the Lavin Declarations—he repeatedly admitted on cross-examination that he is "not qualified" to render an opinion regarding the patent prosecution or the reasons for the allowance of the Asserted Claims. *See* Trial Tr. 904:16–908:20 (Heinecke Cross). Dr. Heinecke admitted that he is not qualified to answer questions regarding (1) the Notice of Allowance, *id*. at 907:23–908:3; (2) whether the Examiner relied on the Lavin Declaration in allowing the Asserted Claims, *id*. 908:4–16; or (3) even on the substance of the Lavin Declaration itself, *id*. 908:17–20. Indeed, Dr. Heinecke admitted that he has not "read through [the Notice of Allowance] carefully enough to say" whether the Examiner even cited to the Lavin Declaration in the Notice of Allowance. Trial Tr. 907:16–22 (Heinecke Cross). Therefore, Defendants offered no reliable testimony regarding the effect of the Lavin Declarations on the allowance of the Asserted Claims.

F. Prior Art

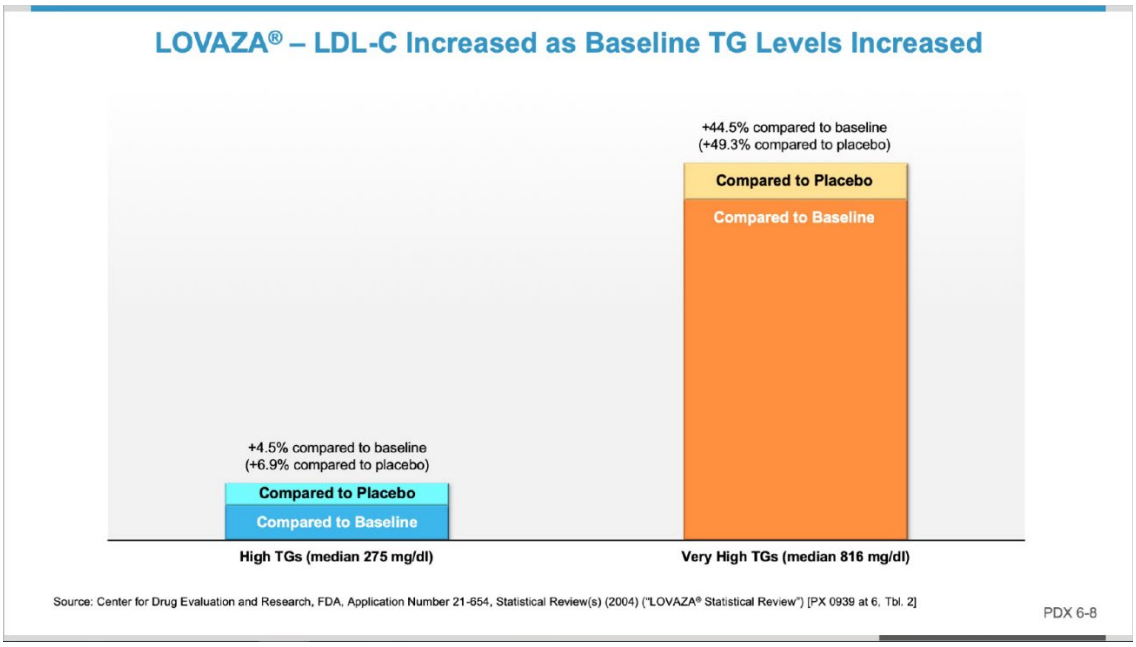
1. Description of Defendants' "Key" Prior Art

a) Lovaza PDR (DX 1535)

545. The Lovaza PDR is the prescribing information for LOVAZA®. DX 1535 (Lovaza PDR). In March 2008, Lovaza was the only prescription omega-3 fatty acid approved by FDA for lowering TGs in patients with severe hypertriglyceridemia, with an indication as "an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥ 500 mg/dL) triglyceride levels." *Id*. at 3; Trial Tr. 1721:3–1722:1 (Toth Direct). Lovaza's active ingredient is "a mixture of omega-3 acid ethyl esters." Trial Tr. 1785:16–1786:5 (Toth Cross); *see also* DX 1535 (Lovaza PDR) at 2. The principal components of that mixture are approximately 465 mg EPA and 375 mg DHA. DX 1535 (Lovaza PDR) at 2. Lovaza had also previously been known and marketed as Omacor. Trial Tr. 730:16–23 (Heinecke Direct). Clinical trial results of Omacor/Lovaza had been reported by 1997. *See* DX 1531 (Harris 1997). A version of the Lovaza prescribing information

was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 021 ('728 Patent) at 8.

546. Lovaza was associated with a large increase in LDL-C in patients with severe hypertriglyceridemia, which posed concerns about atherosclerosis. Trial Tr. 746:20–747:1 (Heinecke Direct). As reported in its prescribing information, and summarized in PDX 6-8 below, Lovaza increased LDL-C in patients with severe hypertriglyceridemia by almost 50% compared to placebo.



547. Because Lovaza increased LDL-C to such a degree in patients with severe hypertriglyceridemia, the Lovaza prescribing information warned physicians that patients "should be monitored to ensure that the LDL-C level does not increase excessively." DX 1535 (Lovaza PDR) at 3.

548. The Lovaza prescribing information did not attribute the rise in LDL-C in patients with severe hypertriglyceridemia to either DHA or EPA alone, nor would a person of ordinary skill in the art have attributed Lovaza's large LDL-C increase to either EPA or DHA. *See* Trial Tr. 1639:10–1640:9 (Toth Direct); *see also* Trial Tr. 829:16–18 (Heinecke Cross) ("The Lovaza PDR does not describe the effects of any particular omega-3 fatty acid."). Instead, a person of ordinary

skill would have attributed the dramatic rise in LDL-C to the TG-lowering mechanism of omega-3 fatty acids generally, and to the very high baseline TG levels of severely hypertriglyceridemic patients, as it was understood that the degree of LDL-C increase was closely correlated to the pretreatment triglyceride levels. *See* Toth Tr. 1665:15–1667:10 (Toth Direct). Consistent with that understanding, Lovaza produced much smaller LDL-C increases in individuals with lower TG levels. *See* PDX 6-8; *see also* PX 939 (Lovaza Statistical Review) at 6, Tbl. 2 (showing that Lovaza increased LDL-C by a median of 4.5% from baseline in patients with high TGs and by 6.9% compared to placebo).

b) Mori 2000 (DX 1538)

549. Mori 2000 reported the results of a double-blind, placebo-controlled trial comparing the effects of 4 g/day EPA versus 4 g/day DHA on 59 overweight mildly hyperlipidemic men. DX 1538 (Mori 2000) at 1; *see also* Trial Tr. 1640:10–1641:7 (Toth Direct). Mori 2000's sample size was small, with 19 subjects taking purified EPA, 17 subjects taking DHA, and 20 subjects taking a placebo. *See* DX 1538 (Mori 2000) at 3, Tbl. 1; *see also* Trial Tr. 1641:8–25 (Toth Direct) (characterizing Mori 2000 as a "small" study). Mori 2000 was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 021 ('728 Patent) at 9.

550. Mori 2000 did not study the effects of purified EPA or DHA in persons with triglyceride levels of at least 500 mg/dL. The patients in Mori 2000 had moderately elevated TGs and LDL-C—with a mean TG level of 178 mg/dL (2.01 mmol/L) and LDL-C level of 166 mg/dL (4.28 mmol/L) for patients administered EPA, and a mean TG level of 199 mg/dL (2.25 mmol/L) and LDL-C level of 165 mg/dL (4.27 mmol/L) for patients administered DHA. *See* DX 1538 (Mori 2000) at 4, Table 2; *see also* Trial Tr. 1642:12–1644:1 (Toth Direct). That is, the patients in Mori 2000 had mixed dyslipidemia. Trial Tr. 830:22–831:3 (Heinecke Cross). Mori 2000 therefore did not teach or create an expectation that high-purity EPA would avoid substantial LDL-C increases in patients with severe hypertriglyceridemia. *See* Trial Tr. 1643:13–19 (Toth Direct) ("[The subjects in Mori 2000] are borderline high triglyceride patients. And we've already established that the patients with very high triglycerides have a very different LDL response."); *see also* Trial

Tr. 831:4–832:5 (Heinecke Cross) (acknowledging that a POSA would understand patients with hypertriglyceridemia to be "entirely different" from patients with mixed dyslipidemia).

551. Mori 2000 reported a variety of lipid effects of EPA, DHA, and placebo. Among such results, Mori 2000 reported that in patients administered DHA that the mean LDL-C level increased from 165 mg/dL (4.27 mmol/L) at baseline to 179 mg/dL (4.64 mmol/L) post-intervention, and that for patients administered EPA, the mean LDL-C level increased from 166 mg/dL (4.28 mmol/L) at baseline to 172 mg/dL (4.46 mmol/L) post-intervention. *See* DX 1538 (Mori 2000) at 4, Tbl. 2; *see also* Trial Tr. 1642:20–1643:2 (Toth Direct). Thus, LDL-C increased both for patients administered DHA (by 8%) and EPA (by 3.5%). *See* Trial Tr. 1643:1–2 (Toth Direct) ("Numerically they both increased.").

552. A person of ordinary skill in the art reviewing these results would not have distinguished the LDL-C effects of EPA from those of DHA on the basis of these results. While the LDL-C increase was only statistically significant in the DHA arm, the person of ordinary skill in the art would have attributed the absence of a statistically significant increase in the EPA arm to (1) the study's small sample size (19 patients in the EPA group and 17 patients in the DHA group) and (2) the difference in the baseline TG levels of the two groups, with the EPA group having a mean TG level 11% lower than the DHA group (2.01 mmol/L or 178 mg/dL for the EPA group versus 2.25 mmol/L or 199 mg/dL for the DHA group). *See* Trial Tr. 1643:20–1645:1 (Toth Direct); *see also* DX 1538 (Mori 2000) at 4, Tbl. 2. Nor did prior art reviewing Mori 2000 distinguish DHA and EPA on the basis of their LDL-C effects. *See* DX 1605 ("von Schacky") at 9, Tbl. I (Table showing that DHA and EPA were understood to have the same effect on LDL-C).

553. Mori 2000 would not have motivated a person of ordinary skill in the art to eliminate DHA and obtain high purity EPA for treatment of severe hypertriglyceridemia. Trial Tr. 1651:1–9 (Toth Direct). Mori 2000 taught that DHA was at least as good as EPA at lowering TGs, and that it had advantages over EPA in terms of other factors understood to affect cardiovascular risk. Trial Tr. 1644:12–1651:13 (Toth Direct).

554. *First*, Mori 2000 taught that EPA offered no advantage over DHA in terms of TG-lowering capability. Trial Tr. 1644:22–1645:5 (Toth Direct). Mori 2000 observed a nominally greater reduction in triglycerides with DHA than EPA. *See* DX 1538 (Mori 2000) at 3 ("After adjustment for baseline values, fasting triacylglycerols [(triglycerides)] decreased significantly by 18.4% with EPA (P = 0.012) and by 20% with DHA (P = 0.003), relative to the placebo group."); *see also* Trial Tr. 1644:12–21 (Toth Direct). A person of ordinary skill reviewing Mori 2000 therefore would not have been motivated to select a composition of purified EPA and substantially no DHA on the basis of TG-lowering considerations. *See* Trial Tr. 1644:22–1645:1 (Toth Direct).

555. *Second*, Mori 2000 observed that, in multiple respects, DHA offered advantages over EPA in terms of cardiovascular benefits. *See* Trial Tr. 1644:12–1651:13 (Toth Direct). Mori 2000 taught that DHA has more favorable effects on lipids than EPA, reporting that "*DHA, but not EPA, improved serum lipid status*, in particular a small increase in HDL cholesterol and a significant increase in HDL_2-cholesterol subfraction, without adverse effects on fasting glucose concentrations." DX 1538 (Mori 2000) at 4 (emphasis added); *see also* Trial Tr. 1645:6–1651:13 (Toth Direct). Mori 2000 also stated that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable." DX 1538 (Mori 2000) at 8. Mori 2000 also noted that "only EPA increased fasting glucose." *Id.*

556. ***HDL cholesterol.*** Mori 2000 reported that, unlike EPA, DHA reported "a small increase in HDL cholesterol and a significant increase in HDL_2-cholesterol subfraction . . . ." *Id.* at 4; *see also* Trial Tr. 1645:6–1646:17 (Toth Direct). Mori 2000 observed that, "[i]n epidemiological terms, the increase in HDL_2 cholesterol could have a marked effect on the incidence of cardiovascular disease, given that HDL_2 cholesterol may be the subfraction of HDL cholesterol that may be most protective against coronary heart disease." DX 1538 (Mori 2000) at 6.

557. In March 2008, a person of ordinary skill in the art would have understood that an increase in HDL would be beneficial. *See* Trial Tr. 1646:10–17 (Toth Direct) ("[i]n March of 20008, it would have been viewed as a positive, if the HDL cholesterol level rose and specifically,

at the time, in general, the HDL_2-cholesterol sub fraction was viewed as the most beneficial sub fraction of HDL."); Trial Tr. 1162:7–10 (Fisher Cross) ("Q. Now, in March of 2008, it was still thought beneficial, from a cardiovascular perspective, to increase HDL cholesterol, correct? A. Yes.")

558. During his direct examination, Dr. Heinecke cited the ATP-III in an effort to diminish the import of HDL-C. Trial Tr. 792:8–793:8 (Heinecke Direct). But Dr. Heinecke admitted on cross-examination that, in 2008, there was an "intense interest" in raising HDL and that enormous financial resources and time were poured into an HDL-raising approach to reduce cardiovascular risk well past 2008. *See* Trial Tr. 902:21–903:1; 903:13–17 (Heinecke Cross); *see also* Trial Tr. 1162:7–15 (Fisher Cross) (acknowledging that in March 2008 it was still thought beneficial to increase HDL and that the pharmaceutical industry was attempting to develop drugs to raise HDL).

559. ***LDL particle size***. Mori 2000 also reported that "[n]either olive oil [the placebo] nor EPA had a significant effect on LDL particle size, whereas DHA supplementation significantly increased LDL particle size." DX 1538 (Mori 2000) at 6; *see also* Trial Tr. 1649:13–1650:20 (Toth Direct). Mori observed that an increase in LDL particle size "might be expected to contribute to a reduction in atherogenic risk." DX 1538 (Mori 2000) at 6.

560. As of March 2008, a person of ordinary skill in the art would have believed that LDL particle size was important to cardiovascular health. *See* Trial Tr. 1649:13–1650:20 (Toth Direct). Studies had shown that "[l]arger particles appeared to be less atherogenic," "[s]maller particles more atherogenic," that "there was evidence that smaller particles would . . . undergo changes such as oxidation that might make them more atherogenic" and that they would "also have a greater difficulty being cleared." Trial Tr. 1649:13–1650:20 (Toth Direct).

561. Dr. Heinecke also attempted to diminish the import of LDL particle size by citing a sentence in the ATP-III stating that it did "not recommend measure of small LDL particles in routine practice." Trial Tr. 793:19–20 (Heinecke Direct). But the preceding sentence (that Dr. Heinecke failed to cite) noted that this was in part because "standard and inexpensive

methodologies [were] not available for their measure." DX 1876 (ATP-III) at 39 PX 989 (ATP-III) at 42. Moreover, ATP-III noted that the presence of small LDL particles "is associated with an increased risk for [coronary heart disease]." *Id.*

562. ***Fasting glucose***. Mori 2000 reported that both EPA and DHA increased fasting insulin, but that only EPA increased fasting glucose. *See* DX 1538 (Mori 2000) at 8; *see also* Trial Tr. 1647:24–1649:12 (Toth Direct). In March 2008, a person of ordinary skill in the art would have understood that an increase in fasting glucose could "be a manifestation of insulin resistance"; "have adverse effects on arterial walls"; and "also contribute to the development of atherosclerotic disease." Trial Tr. 1648:3–1648:13 (Toth Direct). An increase in fasting glucose would have been of particular concern to patients with diabetes, who make up a "good percentage" of patients with severe hypertriglyceridemia. *See* Trial Tr. 1648:18–1649:7 (Toth Direct). Accordingly, the differential effects of EPA and DHA on fasting glucose reported by Mori 2000 would not have led the person of ordinary skill to use EPA, and no DHA, to treat patients with severe hypertriglyceridemia, but instead would have pointed away from use of high purity EPA. *See* Trial Tr. 1649:8–12 (Toth Direct).

563. Dr. Heinecke testified that at the time of ATP-III, fasting blood glucose was not "strongly" considered to be a cardiovascular risk. Trial Tr. 794:3–5 (Heinecke Direct). But Dr. Heinecke acknowledged on cross-examination that fasting glucose was an important cardiovascular risk factor for diabetics; that many patients with severe hypertriglyceridemia have diabetes; and that a person of ordinary skill would not have wanted to develop a treatment for severe hypertriglyceridemia that harmed diabetic patients. Trial Tr. 903:25–904:9 (Heinecke Cross).

c) Hayashi (DX 1532)

564. Hayashi, another small study, examined the effects of 1.8 g/day of EPA in 28 Japanese patients with "familial combined hyperlipidemia." *See* DX 1532 (Hayashi) at 4; *see also* Trial Tr. 1651:20–1652:4 (Toth Direct). Hayashi was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 21 ('728 Patent) at 7.

565. Hayashi was a non-blinded, non-placebo-controlled study in patients with *either* baseline TGs of at least 150 mg/dL *or* starting cholesterol levels of at least 220 mg/dL over an 8-week period. *See* DX 1532 (Hayashi) at 4; *see also* Trial Tr. 1652:8–1653:13 (Toth Direct).

566. Hayashi did not report the lipid effects of purified EPA in persons with TG levels of at least 500 mg/dL, and therefore did not teach or create an expectation that high purity EPA would avoid substantial LDL-C increases in persons with severe hypertriglyceridemia. *See* Trial Tr. 1654:7–21 (Toth Direct). The mean TG level in Hayashi was 300 mg/dL—well below 500 mg/dL. DX 1532 (Hayashi) at 4–5, Tbl. 1; Trial Tr. 1656:18–1658:6 (Toth Direct). Moreover, all, or virtually all, of the subjects in Hayashi had TG levels well below 500 mg/dL. *See* Trial Tr. 1654:22–1658:6 (Toth Direct).

567. Hayashi included correlation graphs in Figure 2, which reported correlations between activities of coagulation factors VII and X and content of plasminogen activator inhibitor-1 (PAI-1) with the plasma TG content of study subjects at week 0. Critically, this figure provides plot points for *individuals* in the study. *See* DX 1532 (Hayashi) at 7, Fig. 2; *see also* Trial Tr. 1655:4–1657:9 (Toth Direct).

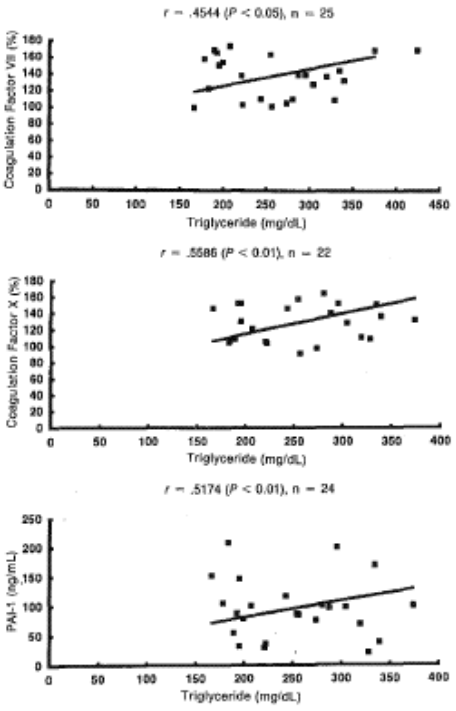


Figure 2. Correlations between activities of coagulation factors VII and X and content of plasminogen activator inhibitor-1 (PAI-1) with plasma triglyceride content at week 0.

568. As shown in these graphs, the highest value on the x-axis (denoting baseline TG levels at week 0) was less than 450 mg/dL. *See* DX 1532 (Hayashi) at 7, Fig. 2; *see also* Trial Tr. 1655:4–1657:9 (Toth Direct). Virtually all plot points fell below 350 mg/dL, with most points falling between 150 and 350 mg/dL, revealing that the large majority of subjects in the study had TG levels below 350 mg/dL. *See* DX 1532 (Hayashi) at 7, Fig. 2; *see also* Trial Tr. 1655:21–1657:9 (Toth Direct). Not a single plot point exceeded 450 mg/dL, let alone 500 mg/dL. *See* DX 1532 (Hayashi) at 7, Fig. 2. Figure 2 thus showed that (1) the overwhelming majority of subjects in the study had TG levels below 400 mg/dL; and (2) at least 25 of the 28 subjects had TG levels below 450 mg/dL. Moreover, because Hayashi did not show any plot point above 500, it demonstrated the absence of any clear indication that any subject had a TG level of at least 500 mg/dL. *See* Trial Tr. 1654:22–1657:9 (Toth Direct).

569. Despite Figure 2, Defendants contend that at least one subject in Hayashi must have had TG levels over 500 mg/dL given that the reported TG mean in Hayashi was 300 ± 233 mg/dL,

see Trial Tr. 752:25–753:5 (Heinecke Direct). On direct examination, Dr. Heinecke opined that "if that is, in fact, a standard deviation, there were many more than that, perhaps as many as four or five." *See* Trial Tr. 752:25–753:5 (Heinecke Direct). But on cross-examination, Dr. Heinecke reluctantly agreed that the plots in Figure 2—which show the TG levels of 25 of the 28 subjects in the study—rule out all but "three mystery patients." *See* Trial Tr. at 894:4–11 (Heinecke Cross). Thus, Dr. Heinecke's opinion that there were at least four patients in Hayashi with TGs levels exceeding 500 mg/dL could not possibly be correct.

570. In addition, given the data in Figure 2, a person of ordinary skill would not have attempted to impute what the TG levels of those mystery patients were. *See* Trial Tr. 1657:13–1658:6 (Toth Direct).

571. Moreover, even if Hayashi had enrolled a few subjects with TG levels of at least 500 mg/dL, there is no indication that LDL-C data was measured in, or reported for, such subjects. *See* Trial Tr. 1658:1–6 (Toth Direct). Hayashi provided no breakdown of LDL-C results showing that any of the reported values were taken from persons with TG levels of at least 500 mg/dL (DX 1532 at 5, Table 1) and a person of ordinary skill would have understood that the study investigators in Hayashi would not have measured LDL-C in any subjects with TGs of at least 400 mg/dL. *See* Trial Tr. 894:20–895:1 (Heinecke Cross); *see also* Trial Tr. 1658:1–1660:24 (Toth Direct).

572. This conclusion rests upon the method used in Hayashi to determine LDL-C levels—the Friedewald equation—which both sides' experts agreed the person ordinary skill would have recognized cannot be used to determine LDL-C levels of patients with TGs over 400 mg/dL. DX 1532 (Hayashi) at 4; Trial Tr. 799:17–800:1 (Heinecke Direct) ("[the Friedewald] equation is not accurate for triglycerides above 400 milligrams per deciliter."), Trial Tr. 894:14–19 (Heinecke Cross) ("Q: And the Friedewald equation is not valid for TG values over 400. A: Correct."); Trial Tr. 1658:7–1659:9 (Toth Direct); *see also*, *e.g.*, DX 1546 (Saito 1998) at 7, ("[T]his [Friedewald] formula can't be applied when the TG value is greater than or equal to 400 mg/dL . . . .").

573. Because the Friedewald equation could not be used to measure LDL-C in patients with TGs of at least 400 mg/dL, a person of ordinary skill would have understood that the study investigators did not measure LDL-C in such patients. *See* Trial Tr. 1659:18–1660:24 (Toth Direct). Indeed, Dr. Heinecke conceded that Hayashi did not measure LDL-C in patients with TGs over 500 mg/dL and that Hayashi therefore teaches nothing about the effect of EPA on LDL-C values in severely hypertriglyceridemic patients. *See* Trial Tr. 894:14–895:1 (Heinecke Cross).

574. In short, a person of ordinary skill would have understood that the LDL-C results reported in Hayashi did not include results from patients with TG levels of at least 400 mg/dL, much less above 500 mg/dL. And, even if Hayashi had enrolled a subject or two with TG levels of at least 500 mg/dL, the person of ordinary skill in the art would have understood that Hayashi did not report LDL-C results for such subjects. Finally, even if Hayashi had attempted to measure LDL-C for those individuals, a person of ordinary skill would have understood that the results would have been invalid, and could have provided no information about the effects of purified EPA on LDL-C in patients with severe hypertriglyceridemia.

575. Defendants contend that the only reason the Patent Examiner issued the Asserted Patents was that the applicants submitted a declaration from Dr. Lavin stating that there were no subjects in the Hayashi reference with TG levels of at least 500 mg/dL, when according to Defendants, there was at least one subject. But, as noted, Figure 2 in Hayashi—which provided plot points for each individual studied—indicated that at least 25 of the 28 study subjects had TG levels below 450 mg/dL and provided no information about any subject with TG levels of at least 500 mg/dL.

576. Moreover, the Patent Examiner did not rely on the Lavin Declaration—as he would have otherwise cited it in his reasons for allowance. *See supra* ¶¶ 96–108. And the only witness who offered testimony about the prosecution history, Dr. Heinecke, is not a patent law expert and admitted on cross-examination that he is not familiar with the MPEP, and was not qualified to offer any opinions relating to the prosecution history or why the Examiner issued the patents. Trial Tr. 904:16–908:20 (Heinecke Cross). Finally, Defendants' contention that the Lavin declaration

was in error is based on a snippet of deposition testimony, but when the transcript is read as a whole, it is clear that Dr. Lavin did not admit error, testifying after giving the statement quoted by Defendants that he provided the best estimate he could come up with based on the limited information available. Trial Tr. 1965:3–17 (Toth Re-Direct); *see also* Lavin Dep. 111:2–5, 7–12 (Q. "Now, are the calculations and opinions you rendered concerning Hayashi in your second declaration your best estimate you could calculate while being accurate . . .? A. It was the best estimate that I could come up with given that I only had data parameters, the mean and the standard deviation.").

577. Hayashi did not express a preference for EPA over DHA. *See generally* DX 1532 (Hayashi). It did not compare EPA to DHA, or demonstrate that EPA had advantages over DHA in any population. *See generally* DX 1532 (Hayashi); *see also* Trial Tr. 1652:23–1653:18 (Toth Direct) (only one arm in Hayashi study).

d) Kurabayashi (DX 1534)

578. Kurabayashi assessed the efficacy and safety of a combination therapy of EPA and estriol for the treatment of hyperlipidemia in symptomatic menopausal Japanese women. Kurabayashi defined hyperlipidemia as serum total cholesterol of 220 to 280 mg/dL or serum TGs of 150 to 400 mg/dL at baseline. *See* DX 1534 (Kurabyashi) at 2. The study groups in Kurabayashi were treated either with 2 mg daily estriol (72 women) or with a combination of 1.8 g daily EPA and 2 mg daily estriol (69 women). *See id.* No subjects received EPA alone. *See* DX 1534 (Kurabyashi); *see also* Trial Tr 1661:18–1664:10 (Toth Direct). Kurabayashi was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 21 ('728 Patent) at 8.

579. Patients who received EPA in Kurabyashi had a mean baseline TG level of 136 mg/dL. DX 1534 (Kurabayashi) at 4, Tbl. 2. A person of ordinary skill in the art therefore would have understood that the subjects receiving EPA had *normal* TG levels. Trial Tr. 1661:18–1662:22 (Toth Direct). Because Kurabayashi did not study subjects with elevated TG levels, let alone very high TG levels, it could not have altered the strong expectation that administration of highly

purified EPA to persons with severe hypertriglyceridemia would produce large increases in LDL-C. *See id.*

580. Additionally, because Kurabayashi administered EPA in combination with estriol (a lipid-altering agent), a person of ordinary skill would not have been able to draw conclusions about the lipid effects of EPA alone on LDL-C or apo B. *See* Trial Tr. 1662:25–1664:13 (Toth Direct). Although Dr. Heinecke opined that the results do not suggest "any interaction or synergy between estriol and EPA," *see* Trial Tr. 735:21–24 (Heinecke Direct), a person of ordinary skill would have understood, as Dr. Toth (who was trained in OB/Gyn) explained, that estriol is a "complex molecule" and therefore, Kurabayashi does not tell that person "much of anything about EPA alone." Trial Tr. 1664:1–13 (Toth Direct). Moreover, Dr. Heinecke (who does not appear to have received any such training) cited no prior art or other literature to support his position that there was no interaction between the EPA and estriol. *See* Trial Tr. 1664:11–13 (Toth Direct).

581. Nor did Kurabayashi disclose or suggest that EPA reduced apo B in patients with severe hypertriglyceridemia. *See generally* DX 1534 (Kurabyashi). Because Kurabayashi did not study the effect of EPA alone, let alone in a population with severe hypertriglyceridemia, a person of ordinary skill would not have been able to discern the effect that EPA had on apo B, even in the population that Kurabayashi studied. Trial Tr. 1661:18–1664:13, 1778:20–1780:22 (Toth Direct).

582. Nor, finally, did Kurabayashi study the effects of DHA. *See* DX 1534 (Kurabyashi); Trial Tr. 1662:23–24 (Toth Direct). Kurabayashi therefore did not compare purified EPA to DHA and did not teach that high purity EPA offered advantages over DHA or a mixture of DHA and EPA.

e) WO '900 (DX 1525)

583. International Patent Application WO 2008/004900, entitled "Production of Ultrapure EPA and Polar Lipids from Largely Heterotrophic Culture," was published in January 2008. As its title suggests, WO '900 focused on production of ultrapure EPA, and it described "a process for obtaining an eicosapentaenoic acid (EPA)-rich composition for therapeutic or prophylactic use, wherein the process employs a culture of micro-organisms of a type selected for

a capability of largely heterotrophic growth, and a capability of production of EPA, and a capability of photosynthetic lipid production." DX 1525 (WO '900) at 13 ¶¶ 350–354. WO '900 was considered by the USPTO during the prosecution of the Asserted Patents. PX 22 ('728 Patent) at 3.

584. Defendants relied on WO '900 only in challenging Claim 16 of the '728 Patent (not the other Asserted Claims)—and only to argue that this reference disclosed a formulation (among numerous others) in which no fatty acid other than EPA is present in a quantity that is more than about 0.6% by weight of all fatty acids combined. Trial Tr. 769:20–770:16 (Heinecke Direct); DX 1525 (WO '900) at 16 ¶¶ 467–469. Dr. Heinecke did not rely on WO '900 and it contains no discussion of severe hypertriglyceridemia, for clinical guidance.

585. WO '900 did not mention hypertriglyceridemia or severe hypertriglyceridemia, the dose or duration for treating such patients, or why EPA would be beneficial in treating severe hypertriglyceridemia. *See generally* DX 1525 (WO '900). Nor did it mention LDL-C, or describe a method for avoiding large LDL-C increases in persons with severe hypertriglyceridemia. *See id.* WO '900 therefore provided no suggestion that high purity EPA would lower TGs in severely hypertriglyceridemic patients without a substantial increase in LDL-C.

2. Prior Art Concerning EPA

a) Epadel PI 2007 (DX 1528)

586. Epadel PI 2007 is the prescribing information for Epadel Capsules 300, a Japanese product of high purity EPA from 2007. This was the fifth version of the prescribing information for Epadel Capsules 300. DX 1528 (Epadel PI 2007) at 1; Trial Tr. 1674:1–1677:4 (Toth Direct). An earlier version of the Epadel prescribing information was included in the second edition of the Japan Pharmaceutical Reference in 1991–1992. *See* DX 1527 (Epadel JPR 1991). But notwithstanding the fact that highly purified EPA had been known since the early 1990s, no one had developed a method of lowering TGs in patients with severe hypertriglyceridemia using high purity EPA as of March 2008. Trial Tr. 889:20–890:1 (Heinecke Cross). Epadel PI 2007 was

considered by the USPTO during the prosecution of the Asserted Patents. PX 21 ('728 Patent) at 6.

587. The Epadel 2007 Prescribing Information contained a first indication for "[a]rteriosclerotic ulceration, alleviation of pain and feeling cold." DX 1528 (Epadel PI 2007) at 2. A person of ordinary skill would not have understood this indication to concern hypertriglyceridemia or severe hypertriglyceridemia. Trial Tr. 1674:10–21 (Toth Direct).

588. The Epadel 2007 Prescribing Information also contained a second indication for "hyperlipidemia." DX 1528 (Epadel PI 2007) at 2. The reference to "hyperlipidemia" is nebulous and contains no definition of what hyperlipidemia in this context was intended to mean. Trial Tr. 1674:22–1676:1 (Toth Direct).

589. A person of ordinary skill would also have understood from the prior art that in Japan "hyperlipidemia" described TG levels at or below 400 mg/dL, and was different from "severe hyperlipidemia," which latter term referred to TG levels higher than 400 mg/dL. DX 1534 (Kurabayashi) at 4 ("*Hyperlipidemia* was defined as a serum total cholesterol concentration of 220 [to] 280 milligrams per deciliter or a *serum triglyceride concentration of 150 [to] 400 [milligrams per deciliter]*. Women with *severe hypertriglyceridemia* (serum total cholesterol greater than 280 [milligrams per deciliter] or s*erum triglycerides greater than 400 [milligrams per deciliter]*). . . .") (emphasis added); *see also* Trial Tr. 896:16–898:19 (Heinecke Cross).

590. Additional testimony further confirmed that the indication for Epadel was for only mildly elevated TGs, not for patients with severe hypertriglyceridemia. *See* Manku Dep. 40:12–41:15 (explaining that the indication for Mochida's Epadel product was "in the area of mild to moderate levels of triglycerides" with TGs in the range of "120 to 200 milligrams per deciliter"); *see also* Osterloh Dep. 111:24–113:2 (Epadel was not approved for "even very moderately raised hypertriglyceridemia.").

591. Next to the indication for "Hyperlipidemia," the Epadel Prescribing Information 2007 stated that "when an excess of triglycerides are presented, depending on the extent of it, the

dosage may be increased to 900 mg per time and three times daily," for a daily dosage of, at most, 2.7 g/day. DX 1528 (Epadel PI 2007) at 2; Trial Tr. 1675:7–11 (Toth Direct). Nowhere did the prescribing information describe what constitutes "an excess of triglycerides." Trial Tr. 1675:7–1676:1 (Toth Direct). There is also nothing in the passage clearly indicating that in obtaining the indication of hyperlipidemia, EPA was administered to patients with TG levels of at least 500 mg/dL. Trial Tr. 1675:7–1676:1 (Toth Direct).

592. Nor is there anything in the Epadel Prescribing information as a whole clearly indicating that, in obtaining the indication, EPA was administered to patients with TG levels of at least 500 mg/dL. *See generally* DX 1528; Trial Tr. 1675:7–1676:1 (Toth Direct). On cross examination of Dr. Toth, Defendants noted that two of the references in the Epadel label are the Takaku and Matsuzawa references. Trial Tr. 1864:5–21 (Toth Cross); DX 1528 (Epadel PI 2007) at 8–9. But while both references were listed in the Prescribing Information, neither is clearly identified as part of the clinical trials leading to approval. *See generally* DX 1528 (Epadel PI 2007). Moreover, neither of those references provides information about the LDL-C effects in those few patients with TG levels over 500 mg/dL: in Takaku, because it is not clear whether the six excluded subjects included the three subjects with TGs over 500 mg/dL, and in Matsuzawa, because the Friedewald equation was used. *See infra* ¶¶ 612–16, 619.

593. The Epadel Prescribing Information 2007 did not report the LDL-C effects of purified EPA in any population, let alone a population with severe hypertriglyceridemia. DX 1528 (Epadel PI 2007); Trial Tr. 1676:2–6 (Toth Direct). It therefore did not disclose that highly purified EPA reduces TGs in patients with severe hypertriglyceridemia without a substantial increase in LDL-C. Nor did it describe the effects of high purity EPA on apo B in any population. *See* Trial Tr. 1676:7–13 (Toth Direct).

594. Beyond failing to teach that high purity EPA would avoid increasing LDL-C in patients with severe hypertriglyceridemia, the Epadel Prescribing Information 2007 did not teach administering daily doses of 4 g per day of EPA. Trial Tr. 1676:14–1677:4 (Toth Direct). For "hyperlipidemia," it prescribed daily dosages of 1.8 to 2.7 g per day, generally recommending 2

capsules of 600 mg EPA be given three times daily (for a total of 1.8 g per day), and where there is an "excess of triglycerides," up to 2.7 g per day. DX 1528 (Epadel PI 2007) at 2.

b) Rambjør (DX 1961)

595. Rambjør investigated the effects of EPA and DHA on lipid and lipoprotein levels in 49 normolipidemic subjects. DX 1961 (Rambjør) at 3. Rambjør reported data obtained from three separate studies in which subjects took 3 g/day EPA, 3 g/day DHA, or 5 g/day fish oil concentrate for three weeks prior to or after taking 5 g/day olive oil placebo. *Id.* Rambjør was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 21 ('728 Patent) at 10.

596. In Rambjør, the group taking EPA had 25 subjects—6 more subjects than the EPA group in Mori 2000. *See* DX 1961 (Rambjør) at 5; *see also* Trial Tr. 1692:11–25 (Toth Direct). Rambjør found that EPA significantly increased LDL-C levels, and reduced TGs. DX 1961 (Rambjør) at 4, 5, Tbl. 3; *see also* Trial Tr. 1692:16–19 (Toth Direct). On the other hand, DHA did not raise LDL-C by a statistically significant amount. DX 1961 (Rambjør). Rambjør also observed that a previously reported study "concluded that both EPA and DHA were equally hypotriglyceridemic, but that DHA also lowered LDL, while EPA did not." DX 1961 (Rambjør) at 4.

597. Rambjør also reported that DHA had a favorable effect on HDL_2-C levels, significantly increasing such levels. *Id.* at 5, Tbl. 3. EPA had no such effect. *Id.* Rambjør observed that "HDL_2-C levels have been inversely associated with coronary heart disease, and that "n-3 FA-induced increase in this HDL subfraction may contribute to the antiatherogenic potential of fish oils." *Id.* at 5.

c) Mori 1999 (PX 565)

598. Mori 1999 investigated whether there were significant differences in the effects of purified EPA or DHA on ambulatory blood pressure (BP) and heart rate (HR) in humans. PX 565 (Mori 1999) at 2; *see also* Trial Tr. 1686:4–1687:10 (Toth Direct). Mori 1999 was a double-blind, placebo-controlled trial of parallel design in which 59 overweight, mildly hyperlipidemic men

were randomized to 4 g/day of purified EPA, DHA, or olive oil for 6 weeks. PX 565 (Mori 1999) at 2. Mori 1999 was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 21 ('728 Patent) at 9.

599. Mori 1999 observed that "purified DHA, but not EPA, resulted in a significant reduction in [ambulatory] BP and HR compared with placebo." PX 565 (Mori 1999) at 2. The authors concluded that DHA may be the principal omega-3 fatty acid in fish and fish oils that lowers BP and HR in humans. PX 565 (Mori 1999) at 2; *see also* Trial Tr. 1687:14–1688:3 (Toth Direct).

d) Woodman (PX 563)

600. Woodman 2003, which was co-authored by Dr. Mori, reported additional data on the differential effects of EPA and DHA on LDL particle size in hypertensive type 2 diabetic subjects. PX 563 (Woodman) at 1; *see also* Trial Tr. 1684:7–18 (Toth Direct). Woodman 2003 observed that LDL particle size increased after supplementation with DHA, but not EPA, in confirmation of the findings in Mori 2000. PX 563 (Woodman) at 1; *see also* Trial Tr. 1684:19–11 (Toth Direct). In reviewing the prior art, Woodman 2003 noted that "[s]upplementation with purified DHA increases LDL particle size, reduces serum triglycerides, and increases HDL_2 cholesterol, as well as improves vascular function and blood pressure." PX 563 (Woodman) at 1; *see also* Trial Tr. 1685:12–1686:3 (Toth Direct). The study concluded that for subjects with type 2 diabetes, "DHA may have more therapeutic value than EPA as a food additive." PX 563 (Woodman) at 1; *see also* Trial Tr. 1685:12–1686:3 (Toth Direct). This would have been of import in the treatment of severe hypertriglyceridemia, because many patients with severe hypertriglyceridemia have diabetes. *See* Trial Tr. 1648:18–1649:7 (Toth Direct).

e) Grimsgaard (DX 1530)

601. Grimsgaard, published in 1997, reported on a 7-week, double-blind, placebo-controlled study to compare the effects of 3.8 g/day EPA versus 3.6 g/day DHA on serum lipids, apolipoproteins, and serum phospholipid fatty acids in humans. DX 1530 (Grimsgaard) at 1.

Grimsgaard was considered by the USPTO during the prosecution of the patents at issue. *See* PX 21 ('728 Patent) at 6.

602. Grimsgaard did not report that purified EPA reduces TGs in persons with severe hypertriglyceridemia without a substantial increase in LDL-C. *See generally* PX 1530 (Grimsgaard). Grimsgaard was not directed to the very-high triglyceride population. The mean baseline TG level of the subjects was 110 mg/dL (1.24 mmol/L) for those receiving DHA and 109 mg/dL (1.23 mmol/L) for those receiving EPA. *See* DX 1530 (Grimsgaard) at 5, Tbl. 4.

603. Defendants contend that Grimsgaard disclosed decreases in LDL-C and apo B with EPA treatment. *See* Trial Tr. 728:13–19 (Heinecke Direct). But Grimsgaard did not study these effects in persons with severe hypertriglyceridemia, and the LDL-C effects of EPA were not significantly different from DHA. *See* DX 1530 (Grimsgaard 1997) at 5, Tbl. 4; *see also* Trial Tr. 728:15–19 (Heinecke Direct). Moreover, while Grimsgaard reported that EPA showed a statistically significant decrease in apo B compared to baseline, statistical significance was not reached when EPA was compared to placebo. *See* DX 1530 (Grimsgaard) at 5, Tbl. 4.

604. Moreover, Grimsgaard taught that there were advantages with using DHA over EPA. Grimsgaard reported that both DHA and EPA reduced TGs in individuals with normal TGs, but that "DHA consistently had a more pronounced triacylglycerol [(triglyceride)]-lowering effect than EPA across all baseline concentrations of triacylglycerol." *Id.* at 6. Grimsgaard also confirmed previous studies which "suggested that serum HDL cholesterol is better maintained with oil rich in DHA than oil rich in EPA." *Id.*

605. Grimsgaard reported that the LDL-C effects of EPA and DHA were not significantly different. Table 4 reported the effects on serum lipids and apolipoproteins with DHA, EPA, and placebo corn oil, and revealed no significant difference between DHA, EPA, and placebo's effect on LDL-C or apo B levels. *See id.* at 5.

f) von Schacky (DX 1605)

606. von Schacky, published in 2006, reviewed prior studies that investigated the effects of DHA and EPA on cardiovascular prevention and treatment of hypertriglyceridemia and

provided, in Dr. Heinecke's words, a "summary of the author's interpretation of what the literature show[ed]." PX 1605 (von Schacky) at 1; Trial Tr. 785:3–12 (Heinecke Direct); *see also* Trial Tr. 1698:2–16 (Toth Direct). von Schacky was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 21 ('728 Patent) at 12.

607. von Schacky recounted what the art had reported about the serum lipid effects of DHA and EPA. *See generally* DX 1605 (von Schacky). With respect to LDL-C, von Schacky reported that with EPA and DHA "[r]ather consistently, LDL has been seen to be increased." DX 1605 (von Schacky) at 5; *see also* Trial Tr. 1947:20–1948:15 (Toth Re-Direct). von Schacky also summarized observations about DHA and EPA in Table I:

Table I Effects of purified eicosapentaenoic and docosahexaenoic acid, as observed in human studies, only significant differences were considered for inclusion. Arrows reflect semi-quantitatively the findings from the literature

	EPA	DHA
Triglycerides	↓↓	↓↓
Cholesterol	↔	↔
LDL	↑	↑
HDL	↔?	↑?
platelet aggregability	(↓)	↓
mean platelet volume	↓	↔
blood pressure	↔	↓
heart rate	↓	↓↓
endothelial function	↔	↑
glucose metabolism	↔	↔

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Note: Information sourced from von Schacky and Weber 1985; Nozaki et al 1992; Rambjor et al 1996; Grimsgaard et al 1997, 1998; Mori, Bao, et al 1999; Mori, Burke, et al 2000; Mori, Watts, et al 2000; Woodman et al 2000, 2002, 2003a, 2003b; Park and Harris 2002; Mori and Woodman 2006.

608. The table reported that DHA and EPA had similar effects of increasing LDL-C , and that DHA was understood to have advantages over EPA in terms of effects on HDL, platelet aggregability, blood pressure, heart rate, and endothelial function. DX 1605 (von Shacky) at 9, Tbl. 1; *see also* Trial Tr. 1698:23–1703:2 (Toth Direct).

609. Dr. Heinecke attempted to belittle von Schacky as a "review" with "no primary data" in the paper. Trial Tr. 785:3–10 (Heinecke Direct). But as both Drs. Heinecke and Toth agreed, this publication was a synthesis "of what the literature showed" about the relative effects of DHA and EPA. Trial Tr. 785:3–12 (Heinecke Direct); Trial Tr. 1698:10–16 (Toth Direct). It is therefore entitled to a great deal of weight in determining how the person of ordinary skill, reviewing the art as a whole, would have assessed the comparative attributes of DHA and EPA.

610. Defendants also attempted to discredit the von Schacky reference on the ground that its conclusions were semi-quantitative, and that the arrows showing directional effects of DHA and EPA were supposedly "totally unclear." Trial Tr. 785:13–786:14 (Heinecke Direct). But a person of ordinary skill would have found a semi-quantitative evaluation helpful because one can tell quickly by looking, based on the number and direction of arrows, how DHA and EPA compare on a variety of effects. Trial Tr. 1701:12–22 (Toth Direct). And from the comparison, it is clear that EPA was not understood to have *any* advantages over DHA, but that DHA *was* understood to have advantages over EPA in several respects. Trial Tr. 1702:19–1703:2 (Toth Direct).

611. Defendants also point to a statement in the text of von Schacky stating that in Mori 2000 "no effects of either EPA or DHA" were seen on LDL-C. DX 1605 (von Schacky) at 5. But elsewhere in the article, under a heading discussing DHA and EPA, von Schacky reported that "[r]ather consistently, LDL has been seen to be increased with a few exceptions" with both DHA and EPA, thereby strongly supporting the conclusions in Table 1 that, on the whole, both EPA and DHA were understood to raise LDL-C. DX 1605 (von Schacky) at 4–5; Trial Tr. 1947:25–1948:21 (Toth Re-Direct).

3. Art Purportedly Describing Treatment of Severe Hypertriglyceridemia with EPA

a) Takaku (DX 1550)

612. Takauku reported the results of a study conducted in which EPA was administered to 33 hyperlipidemic patients. DX 1550 (Takaku) at 12; Trial Tr. 1670:14–24 (Toth Direct). Dr. Heinecke testified that Takaku disclosed that three subjects had TG levels above 500 mg/dL, and

that the administration of the highly-purified EPA showed "no significant fluctuation" in LDL-C. Trial Tr. 720:1–722:4 (Heinecke Direct).

613. But Takaku did not teach anything about the effect of purified EPA on LDL-C in severely hypertriglyceridemic patients. Although there were three subjects who had TG levels above 500 mg/dL, the mean baseline TG level of the patients in the study was 245 mg/dL, and nowhere did the Takaku paper provide information about the effect of medication on LDL-C in patients with very high TGs. DX 1550 (Takaku) at 3; Trial Tr. 1671:3–9 (Toth Direct).

614. Moreover, Takaku excluded six subjects from the LDL-C results because measurement was not feasible due to "insufficient sample." DX 1550 (Takaku) at 21; Trial Tr. 1671:10–16 (Toth Direct). There is no evidence that the excluded patients did not include those with very high TG levels. Trial Tr. 1671:17–1672:11 (Toth Direct). Thus, it is unclear if LDL-C was measured in even a single subject with TGs of at least 500 mg/dL. *Id.*

615. Additionally, Takaku did not clearly disclose the method by which LDL-C levels were measured. Trial Tr. 1672:9–11 (Toth Direct). To the extent the Friedewald equation was used, a person of ordinary skill would have recognized that it would not have accurately measured LDL-C in patients with TG levels of at least 400 mg/dL (or that such patients were among those who were "excluded"). *See supra* ¶¶ 572–73.

616. Takaku did not study the effects of DHA or state that EPA had advantages over DHA or an EPA/DHA mixture. *See generally* DX 1550 (Takaku). It would have provided no motivation to modify Lovaza® to use high purity EPA in persons with very high TGs.

b) Saito 1998 (DX 1546)

617. Dr. Heinecke testified that Saito 1998 (DX 1546) disclosed administration of EPA to a single subject with TG levels of 513 mg/dL. Trial Tr. 732:13-733:5 (Heinecke Direct). But only 1 of 12 subjects in Saito 1998 had TG levels of at least 500 mg/dL, and the average baseline TG level of those subjects was 295 mg/dL. DX 1546 (Saito 1998) at 12, 16; Trial Tr. 1673: 13–18 (Toth Direct). Moreover, the LDL-C levels of the subjects were estimated using the Friedewald equation. *Id.* at 7; Trial Tr. 1673: 13–18 (Toth Direct). Because "this formula can't be applied

when the TG value is greater than or equal to 400 mg/dL," DX 1546 at 7, Saito specifically excluded patients with TGs of at least 400 mg/dL from the LDL-C determination. *Id*. Any reported LDL-C results therefore did not include subjects with baseline TG levels of 500 mg/dL, and Saito 1998 did not teach that high purity EPA lowers TGs in persons with severe hypertriglyceridemia without substantially increasing LDL-C. Trial Tr. 1673:13–18 (Toth Direct).

618. Saito 1998 did not compare the effects of DHA to EPA in the study, and did not teach advantages of EPA over DHA. *See generally* DX 1546 (Saito 1998). Neither it, nor the Defendants' other references, would have motivated a person of ordinary skill to use high purity EPA in persons with severe hypertriglyceridemia.

c) Matsuzawa (DX 1537)

619. Dr. Heinecke testified that at least one subject administered EPA in Matsuzawa had TG levels exceeding 500 mg/dL. Trial Tr. 722:25–723:21 (Heinecke Direct). But in Matsuzawa, only one of 26 subjects had TG levels exceeding 500 mg/dL. *See* DX 1537 (Matsuzawa) at 7, 11, 23; Trial Tr. 1673:6–12 (Toth Direct). And the mean TG level of the subjects in Matsuzawa was 308 $\pm$ 70 mg/dL—well below 500 mg/dL. DX 1537 (Matsuzawa) at 7. While four patients enrolled in the study had TG levels of at least 400 mg/dL, Matsuzawa excluded them from the LDL-C calculation. DX 1537 (Matsuzawa) at 11, 23; Trial Tr. 1673:6–12 (Toth Direct). Matsuzawa taught nothing about the effects of high purity EPA on LDL-C in persons with severe hypertriglyceridemia, and would not have motivated a person of ordinary skill to use high purity EPA in severely hypertriglyceridemic patients.

d) Nakamura (DX 1539)

620. Dr. Heinecke testified that Nakmura 1999 disclosed administration of EPA to a subject with baseline TGs of 560 mg/dL. Trial Tr. 733:6-734:3 (Heinecke Direct). But Nakamura was not directed to a population with severe hypertriglyceridemia, as the mean baseline TG level was 183 mg/dL, and only 1 of 14 subjects had TG levels of at least 500 mg/dL. *See* DX 1539 (Nakamura) at 2; Trial Tr. 1673:1–5 (Toth Direct). Moreover, Nakamura did not report any LDL-C results for any subjects. *See* DX 1539 (Nakamura) at 2; Trial Tr. 1673:1–5 (Toth Direct).

4. JELIS Prior Art

a) Yokoyama 2007 (DX 1553)

621. Yokoyama, published in 2007, reported results from the JELIS study, an open-label trial that investigated whether the long-term use of EPA (1.8 g/day with, in certain patients, a low-dose statin) is effective for prevention of major coronary events in hypercholesterolaemic patients in Japan who consume a large amount of fish. *See generally* DX 1553 (Yokoyama 2007). 3,664 Japanese subjects with coronary artery disease (for secondary prevention) and 14,981 Japanese subjects without coronary heart disease (for primary prevention) were randomly assigned to receive EPA with statin or statin alone. DX 1553 (Yokoyama 2007) at 2. Yokoyama was considered by the USPTO during the prosecution of the patents at issue. PX 21 ('728 Patent) at 13.

622. The subjects in JELIS had a median baseline TG level of 153 mg/dL (1.73 mmol/L)—barely above normal; there is no indication that any subjects had TGs of at least 500 mg/dL. DX 1553 (Yokoyama 2007) at 3, Tbl. 3; Trial Tr. 1744:2–1745:15 (Toth Direct); Tr. 1120:7–12 (Fisher Cross). JELIS therefore would have told a person of ordinary skill nothing about the effects of EPA on LDL-C in patients with severe hypertriglyceridemia, or on cardiovascular risk reduction.[15] Trial Tr. 1745:6–21, 1769:1–1770:9 (Toth Direct); *see also* Trial Tr. 1949:2–1951:19, 1957:24–1959:3 (Toth Re-Direct). Indeed, a person of ordinary skill in the art as of 2008

[15] This is also evident from Dr. Fisher's testimony. He testified that even with the published results of REDUCE-IT, it was not clear to him that VASCEPA provides benefit in severely hypertriglyceridemic patients. Trial Tr. 1108:11–15 (Fisher Cross); *but see id.* at 1108:16–21 (Fisher Cross) (acknowledging that he had not studied the REDUCE-IT Clinical Study Report on the issue). Certainly then, the person of ordinary skill would not have reasonably expected from JELIS in March 2008 that EPA would confer a cardiovascular benefit in patients with very high TGs. The population studied in JELIS had a lower mean baseline TG level than that studied in REDUCE-IT, and JELIS did not include patients with very high TGs. *See generally* DX 1553 (Yokoyama); Trial Tr. 1744:2–1745:15 (Toth Direct); Trial Tr. 1957:24–1959:3 (Toth Re-Direct). Additionally, as of March 2008, and prior to the MARINE study, a person of ordinary skill would have expected that EPA would cause large LDL-C increases in patients with severe hypertriglyceridemia, which would exacerbate cardiovascular risk rather than reduce it. Trial Tr. 1574:2–21, 1577:13–1578:11, 1769:1–1770:9 (Toth Direct); *see also* Trial Tr. 1949:2–1951:19, 1957:24–1959:3 (Toth Re-Direct).

would not have expected that any potential cardiovascular benefits reported in JELIS would be applicable to persons with TG levels of at least 500 mg/dL; to the contrary, a person of ordinary skill would have expected that purified EPA, like omega-3 fatty acids generally, would dramatically increase LDL-C, thereby exacerbating cardiovascular risk rather than reducing it. Trial Tr. 1574:2–21, 1577:13–1578:11, 1769:1–1770:9 (Toth Direct); *see also* Trial Tr. 1949:2–1951:19, 1957:24–1959:3 (Toth Re-Direct).

623. The primary endpoint in JELIS was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. DX 1553 (Yokoyama 2007) at 2; Trial Tr. 1749:22–1750:3 (Toth Direct). After a mean follow-up period of 4.6 years, major coronary events were reported as reduced by 19% in the EPA group. DX 1553 (Yokoyama 2007) at 1; Trial Tr. 1744:2–1746:4 (Toth Direct). JELIS reported no benefit in terms of stroke reduction or in terms of sudden cardiac death. DX 1553 (Yokoyama 2007) at 5, Fig. 3.

624. JELIS was not embraced as establishing cardiovascular benefit—in any population. Trial Tr. 1743:6–1753:25, 1759:12–1760:23, 1769:1–1770:19 (Toth Direct); PX 994 (Rosebraugh Decl.) at 14–15, ¶¶ 26–27. Among the reasons that JELIS was not embraced were a number of serious design flaws in the study—flaws that FDA recognized. PX 994 (Rosebraugh Decl.) at 14–15, ¶¶ 26-27.

625. While the JELIS trial showed a 19% risk reduction in the primary endpoint, that result was driven by a single, highly subjective, component: unstable angina. DX 1553 (Yokoyama 2007) at 5, Fig.3; Trial Tr. 1750:4–1753:25 (Toth Direct); PX 994 (Rosebraugh Decl.) at ¶¶ 14-15. Unstable angina is a type of chest discomfort caused by poor blood flow through heart. It is a relatively subjective measure because it does not have many objective features; the chest pain experienced by patients is not necessarily attributable to heart pain, but instead could easily be attributable to other things. Trial Tr. 1753:2–19 (Toth Direct).

626. That the overall significant reduction in cardiovascular risk reported in JELIS was driven by unstable angina is evident from Figure 3 in the Yokoyama publication. DX 1553

(Yokoyama 2007) at 5, Fig. 3; Trial Tr. 1750:13–1752:16 (Toth Direct). Figure 3 plots estimated hazard ratios of clinical endpoints stratified by prevention stratum, listing error bars (denoting margins of error) for the hazard ratio of each of the components of the primary endpoint for "Major coronary event." DX 1553 (Yokoyama 2007) at 5, Fig. 3. Only those error bars that are completely to the left of, and do not cross, 1 (or "unity") favor EPA to a statistically significant degree. Trial Tr. 1750:10–1752:13 (Toth Direct). Figure 3 (highlighting added) appears directly below:

Event	Number (%) of patients		p value	Hazard ratio (95 %CI)
	Control	EPA		
All patients				
Major coronary events	324 (3·5)	262 (2·8)	0·011	0·81 (0·69–0·95)
Items of account				
Sudden cardiac death	17 (0·2)	18 (0·2)	0·854	1·06 (0·55–2·07)
Fatal MI	14 (0·2)	11 (0·1)	0·557	0·79 (0·36–1·74)
Non-fatal MI	83 (0·9)	62 (0·7)	0·086	0·75 (0·54–1·04)
Unstable angina	193 (2·1)	147 (1·6)	0·014	0·76 (0·62–0·95)
CABG or PTCA	222 (2·4)	191 (2·1)	0·135	0·86 (0·71–1·05)
Combined endpoint				
Coronary death or MI	113 (1·2)	88 (0·9)	0·083	0·78 (0·59–1·03)
Fatal MI or nonfatal MI	93 (1·0)	71 (0·8)	0·091	0·77 (0·56–1·05)
Coronary death	31 (0·3)	29 (0·3)	0·812	0·94 (0·57–1·56)
Non-fatal coronary events	297 (3·2)	240 (2·6)	0·015	0·81 (0·68–0·96)

627. At the top of the figure, the primary endpoint for "major coronary events" reveals a statistically significant result favoring EPA—*i.e.*, an overall positive outcome for the trial. DX 1553 (Yokoyama 2007) at 5, Fig. 3; Trial Tr. 1751:6–23 (Toth Direct). But when one looks above at the components of that composite outcome, the only component that shows a statistically significant result favoring EPA is unstable angina; the error bar of every other endpoint crosses unity (and has a p-value exceeding 0.05), meaning that none of the other components were statistically different from statin alone. DX 1553 (Yokoyama 2007) at 5, Tbl. 3; Trial Tr. 1750:10–1752:13 (Toth Direct). Thus, the driver for the overall positive outcome in JELIS was unstable angina. Trial Tr. 1750:10–1752:13 (Toth Direct); PX 994 (Rosebraugh Decl) at 14–15, ¶¶ 26–27.

628. That the unstable angina component showed a statistically significant reduction in risk—while no other component of the primary endpoint did—strongly suggests that bias may have influenced the results. Trial Tr. 1752:14–1753:25 (Toth Direct). This is particularly true because, as noted above, unstable angina is a subjective outcome measure that is more susceptible to bias. Trial Tr. 1752:22–1753:19 (Toth Direct); PX 994 (Rosebraugh Decl.) at 14–15, ¶ 26.

629. Bias may have played a role in skewing the results in the JELIS trial because of the study's open-label design. DX 1553 (Yokoyama 2007) at 7; Trial Tr. 1752:17–1753:25 (Toth Direct). Open-label studies are subject to bias, because both the study subjects and trial investigators are aware of what treatment is being administered, and such knowledge can influence their behavior, such as whether and to what extent subjects report symptoms—thereby potentially skewing the results and rendering them unreliable. Trial Tr. 1752:17–1753:25 (Toth Direct). Research has estimated that unblinded studies can result in the reported benefit of a study drug being inflated by up to 17 percent. Trial Tr. 1753:20–25 (Toth Direct).

630. That bias may have influenced the results is further evident given that the only component of the primary endpoint that showed a significant result was unstable angina. Trial Tr. 1752:9–1753:25 (Toth Direct). If the study medication truly did reduce cardiovascular risk in JELIS, one would have expected to see statistically significant reductions in a *variety* of different, more objective components such as myocardial infarction. *Id*. Moreover, in the Yokoyama paper itself, the JELIS study investigators acknowledged that they "[could] not exclude the possibility of bias in some of the physician-initiated endpoints, such as coronary revascularisation and hospital treatment for unstable angina." *See* DX 1553 (Yokoyama 2007) at 7. Accordingly, a person of ordinary skill in the art in March 2008 reviewing the data in Yokoyama would have concluded that bias could have inflated the reported results. Trial Tr. 1752:9–1753:25 (Toth Direct).

631. The possibility of bias from the open-label nature of the JELIS study, coupled with the subjectivity of the unstable angina component, was of major concern to FDA when interpreting the JELIS study. Curtis Rosebraugh, the Director of the Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research of FDA, explained in a 2015 declaration:

> [T]he main component of the primary endpoint in the JELIS trial was unstable angina, which is a more subjective endpoint than, for example, objective major adverse cardiovascular event endpoints (e.g., heart attack, stroke, or cardiovascular death). A subjective endpoint such as unstable angina may be particularly unreliable in

> an open-label trial where patients and physicians are making decisions regarding hospitalizations.

PX 994 (Rosebraugh Decl.) at 14–15, ¶ 26 (emphasis added).

632. JELIS was not understood to have established that Epadel significantly reduced residual cardiovascular risk in any population. This is reflected in the widespread surprise and enthusiasm in late 2018, after publication of the REDUCE-IT results. For instance, in an editorial in the *New England Journal of Medicine*, the authors welcomed the REDUCE-IT results with "surprise, speculation, and hope . . . . After a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events." PX 959 (Kastelein) at 1–2. And leading doctors observed that REDUCE-IT was a "game changer." *See supra* ¶ 170. The results of REDUCE-IT would not have been welcomed with such enthusiasm and surprise if the need for a TG-lowering agent that significantly reduced cardiovascular risk had already been met years earlier by Epadel in JELIS.

633. Other medical literature reflected the understanding that JELIS did not establish that Epadel provides cardiovascular benefit on top of statin. Trial Tr. 1746:5–1749:14 (Toth Direct). For example, an article in *JAMA Cardiology* published after JELIS, but before REDUCE-IT, concluded that there was "no support for current recommendations for the use of [omega-3 fatty acid] supplements in people with a history of coronary heart disease," including purified EPA—even though the authors were aware of JELIS. PX 954 (Aung) at 1, 3; Trial Tr. 1748:16–1749:14 (Toth Direct). Similarly, the well-respected Cochrane Collaboration concluded before REDUCE-IT that "[s]upplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little"—even though these authors were also aware of the JELIS trial. PX 953 (Abdelhamid) at 33, 66; Trial Tr. 1746:9–1748:5 (Toth Direct). If these authors had concluded from JELIS that Epadel significantly lowered residual cardiovascular risk, as Defendants contend, there would have been no such blanket rejection of omega-3 fatty acids.

634. A publication by one of Defendants' experts, Dr. Fisher, further reflects that the JELIS results were not widely embraced by the medical community as establishing that EPA provides cardiovascular benefit—in *any* population.[16] *See* PX 373 (Chapman); Trial Tr. 1127:1–1138:4 (Fisher Cross). This guidance was published in the *European Heart Journal* in 2011 by an "august body" and "well respected" panel of clinicians, and its purpose was to help clinicians manage cardiovascular disease. PX 373 (Chapman); Trial Tr. 1127:12–1131:3 (Fisher Cross). All members of the consensus panel, including Dr. Fisher, were involved in writing the manuscript and approved the final manuscript before submission. PX 373 (Chapman) at 16; Trial Tr. 1129:9–14 (Fisher Cross).

635. Although aware of the results from JELIS, the panel did not recommend EPA or omega-3 fatty acids for addressing atherogenic dyslipidemia (residual cardiovascular risk). PX 373 (Chapman) at 13, 16, 22; Tr. 1134:12–1137:7 (Fisher Cross). Additionally, the authors noted a "lack of hard outcome data" with omega-3 fatty acids for addressing cardiovascular risk. PX 373 (Chapman) at 13, 16; Trial Tr. 1136:8–1137:7 (Fisher Cross).

636. Additionally, after JELIS, but before REDUCE-IT, other guidelines did not recommend high purity EPA to reduce cardiovascular risk. Trial Tr. 1161:17-25 (Fisher Cross). As of 2018, the American Diabetes Association did not recommend EPA. *Id.* But in 2019, after the REDUCE-IT results were announced, the American Diabetes Association changed its guidelines for addressing cardiovascular risk to recommend EPA. *Id.*

637. FDA's 2013 rejection of Amarin's proposed ANCHOR indication for VASCEPA further undercuts Defendants' contention that JELIS established that Epadel met the need for a TG-lowering agent that significantly reduced residual cardiovascular risk. As noted above, Amarin had shown in the ANCHOR trial that VASCEPA lowered TGs in patients with baseline TGs of 200–499 mg/dl, and on that basis sought an indication to administer VASCEPA® to statin-treated

[16] Additionally, following JELIS, Dr. Fisher did not seek out pure EPA treatment, nor was he even motivated to use high purity EPA for his own health. Instead, he took a mixture of DHA and EPA. Trial Tr. 1138:15-1140:5 (Fisher Cross).

patients in this TG range, on the theory that VASCEPA® may provide a cardiovascular benefit to such patients. *See supra* ¶¶ 152–58. But FDA declined to grant the indication without completion of the REDUCE-IT trial, concluding that the available evidence at the time—which included the results from the JELIS trial—was insufficient to conclude that high purity EPA would provide a significant incremental cardiovascular benefit over and above appropriate statin therapy. *See supra* ¶¶ 152–58.

638. Furthermore, the change in VASCEPA labeling before and after REDUCE-IT reveals that FDA did not believe that JELIS established that high purity EPA has a cardiovascular benefit in patients with severe hypertriglyceridemia. After JELIS, but prior to REDUCE-IT, the VASCEPA label specified that "[t]he effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined." PX 940 (VASCEPA Label 2017) at 2. Only following REDUCE-IT was that limitation of use removed. PX 1186 (VASCEPA Label 2019) at 2.

639. Rather than engage with the significant flaws in the JELIS trial—ones acknowledged by both FDA and Yokoyama itself[17]—Defendants focused on statements Amarin made about the JELIS trial as part of its efforts to secure approval for the ANCHOR indication. *See, e.g.*, Trial Tr. 988:18–1005:25 (Fisher Direct). Defendants' reliance on these statements is flawed for several reasons.

640. First, Defendants overlook that the medical community generally—including FDA—did not view JELIS as establishing a cardiovascular benefit in any population, and were troubled by the flaws in the JELIS study design. *See supra* ¶¶ 158, 621–38. For example, while Dr. Fisher emphasized statements in internal documents from Amarin about JELIS, he referenced

[17] Yokoyama itself noted that the JELIS trial had "several limitations." *See* DX 1553 (Yokoyama 2007) at 7–8. These self-acknowledged limitations included that (1) the study could not "exclude the possibilitiy of bias in some of the physician-initiated endpoints, such as coronary revascularisation and hospital treatment for unstable angina"; (2) the study used "low doses of statins" and did not use a "true placebo group"; (3) the study was "substantially underpowered for analysis of subgroups"; and (4) that because the study population was exclusively Japanese, the results could not be generalized to other populations. *See* DX 1553 (Yokoyama 2007) at 7–8.

no published literature citing JELIS as support for using EPA to reduce cardiovascular risk. Tr. 1123:1-5 (Fisher cross). And his own 2011 guidelines did not consider JELIS sufficient to recommend use of EPA to reduce cardiovascular risk in any population. *See supra* ¶¶ 634–35. Moreover, when one "looks under the hood," it is apparent—as it was to FDA—that JELIS has fundamental design flaws—as Dr. Toth explained when acknowledging that he had erred in previously uncritically reporting that the JELIS trial reported a 19% reduction in risk. Trial Tr. 1919:23-1920:1 (Toth Cross) ("I also take responsibility for the fact that I didn't do a great job of looking under the hood for the entire spectrum results in the [JELIS] study, and, instead, I just focused on the primary composite endpoints. And when I say 'looking under the hood,' I didn't do a very critical analysis of all the endpoints that were offered I the study which showed considerable weakness in the study."); *see also* Trial Tr. 1921:4-9 (Toth Cross) ("But JELIS also did not get Epadel any approval in the United States, and the reason for that is that there were weaknesses in the study.").

641. Second, Defendants overlook that the large majority of the Amarin statements were made in 2013 and 2014—"well after 2008"—and after Amarin had conducted both the MARINE and ANCHOR studies. *See* Trial Tr. 1122:15–1126:25 (Fisher Cross). These Amarin statements about JELIS were therefore made through the prism of subsequent work that Amarin had done on EPA, rather than from the vantage of a person of ordinary skill in March 2008.

642. Third, the Amarin statements about JELIS were made in connection with attempts to secure the ANCHOR indication, which was focused on a patient population with TGs below 500 mg/dL—patients with mixed dyslipidemia and coronary heart disease, or coronary heart disease risk equivalent—not for severely hypertriglyceridemic patients. Trial Tr. 1122:20–1126:18 (Fisher Cross). The JELIS trial had nothing to do with treatment of patients with severe hypertriglyceridemia, as the mean TG level of patients receiving EPA was 153 mg/dL, Trial Tr. 1745:6–1745:21 (Toth Direct), and the statements made by Amarin about JELIS therefore had nothing to do with severe hypertriglyceridemia (or what LDL-C effects and cardiovascular risk reduction would be observed in patients with very high TGs). Trial Tr. 1122:15–1126:13 (Fisher

Cross); *see also* Trial Tr. 1745:6–21, 1769:1–1770:9 (Toth Direct); Trial Tr. 1949:2–1951:19, 1957:24–1959:3 (Toth Re-Direct).

643. If JELIS had motivated a person of ordinary skill to pursue an omega-3 fatty acid formulation, it would not have been high purity EPA, but instead one with substantial amounts of DHA. The JELIS trial administered EPA exclusively to Japanese subjects, whose diet is very high in fish consumption—approximately 5 times higher than in other countries. DX 1553 (Yokoyama 2007) at 7; Trial Tr. 1763:4-1764:16 (Toth Direct). Because fish contain natural amounts of DHA, the high fish intake in Japanese persons meant that Japanese subjects in Yokoyama ingested large amounts of DHA through diet alone. Trial Tr. 1763:4–1764:16 (Toth Direct); Trial Tr. 1969:3–8 (Toth Re-Direct); Trial Tr. 1152:23–1153:13 (Fisher Cross).

644. Thus, if a person of ordinary skill had sought to pursue a formulation for a Western population that mimicked composition of omega-3 fatty acids that the Japanese subjects in JELIS actually consumed, that person would have included substantial amounts of DHA. Trial Tr. 1763:1–1764:16 (Toth Direct); Trial Tr. 1969:3–8 (Toth Re-Direct).

645. That a person of ordinary skill in the art would have wanted to pursue a fatty acid formulation with substantial amounts of DHA is further reinforced by other prior art—which taught that DHA has several *advantages* over EPA, *see supra* ¶¶ 553–63, 604, 608–10; *infra* ¶¶ 673–81—and reflected in the fact that all ongoing cardiovascular outcomes trials underway as of March 2008 included formulations containing substantial amounts of DHA. *See supra* ¶¶ 142–51.

646. Yokoyama did not disclose administering 4 g/day of EPA for at least 12 weeks. *See generally* DX 1553 (Yokoyama 2007). Nor would JELIS have motivated a person of ordinary skill to pursue a 4 g formulation. JELIS administered a dose of 1.8 g and all ongoing omega-3 cardiovascular outcome trials underway as of March 2008 used daily doses far below 4 g. *See* DX 1553 (Yokoyama 2007) at 2; *supra* ¶¶ 142–51. Additionally, prior art suggested that a 4 g dose could exceed an optimal threshold or apparently interfere with potential benefits of omega-3 fatty acids at lower doses. *See, e.g.*, PX 567 (Nilsen) at 5 ("It is also possible that the high doses [4 g/day] of concentrated n-3 fatty acids applied in this study exceeded some optimal threshold level,

outweighing the beneficial effect or even leading to an apparent adverse effect."); Trial Tr. 1708:10–1710:23 (Toth Direct). Furthermore, the typical dosing range for TG-lowering was 1.8 to 2.7 grams. Trial Tr. 1857:20–1858:1 (Toth Cross).

647. Amarin later showed that EPA blood levels in patients who took 4 g of VASCEPA were similar to EPA levels in JELIS patients who took 1.8 g of Epadel, but this showing does not alter the analysis. PX 272 (Bhatt) at 9. There was no prior art connecting those blood levels, and that discovery came about only as a result of the work that Amarin did well after 2008. Trial Tr. 1761:11–1762:22 (Toth Direct); Trial Tr. 1153:25–1154:18 (Fisher Cross). And in a Western population consuming only one-fifth as much fish as a Japanese population, a person of ordinary would not have reasonably expected that 4g EPA would be as cardioprotective as 2 g were in a Japanese population. Trial Tr. 1155:10–14 (Fisher Cross).

648. Yokoyama 2007 also did not measure the effect of purified EPA on apo B. *See generally* DX 1553 (Yokoyama 2007). Therefore, no conclusion can be drawn concerning the effects of purified EPA on apo B in any patient population.

b) Saito 2008 (DX 1547)

649. Defendants introduced Saito 2008 for the first time during the cross-examination of Dr. Toth. Trial Tr. 1921:24–1922:22 (Toth Cross); DX 1547 (Saito 2008). But Saito 2008 was published in June 2008 (DX 1547 at 1), and therefore was not prior art. *Id.* at 1.

650. Saito 2008 reported on an analysis of subgroups in the JELIS study, but the JELIS study was not powered for subgroup analysis. DX 1553 (Yokoyama 2007) at 7 ("Third, this trial was substantially underpowered for analysis of subgroups."); Trial Tr. 1104:25-1106:2 (Fisher Cross); Trial Tr. 1921:24-1922:17 (Toth Cross).

651. One of the subgroups in Saito 2008 had "dyslipidemia," defined as having serum TG levels greater than or equal to 150 mg/dL and/or HDL-C levels less than 40 mg/dL. DX 1547 (Saito 2008) at 2. More specifically, this subgroup had a mean baseline TG level of 272 mg/dL, ranging from 207 mg/dL to 399 mg/dL. *Id*. at 4, Tbl. 1. Thus, far from having severe hypertriglyceridemia, the patients in this subgroup were most like the patients with mixed

dyslipidemia (who had moderately elevated TGs) in the Tricor label. *Id*. at 4, Tbl. 1; PDX 6-7; Trial Tr. 1949:2–1953:6 (Toth Re-Direct). Such patients were not prone to the same dramatic LDL-C increases as patients with very high TGs, and thus an analysis of that population would have said nothing about the effects of a TG-lowering agent on LDL-C or cardiovascular risk in patients with very high TGs. *See* Trial Tr. 1949:2–1951:19, 1957:24–1959:3, 1968:11–1969:2 (Toth Re-Direct); *see also* Trial Tr. 1574:2–21, 1577:13–1578:11, 1769:1–1770:9 (Toth Direct); PDX 6-7. Thus, Saito 2008 would have provided no reasonable expectation of avoiding LDL-C increases in severely hypertriglyceridemic patients, or in conferring a reduction in cardiovascular risk in such patients.

652. Moreover, as noted above, a person of ordinary skill would have understood that the JELIS study had a number of underlying flaws that would have undermined confidence in the Saito 2008 results. *See supra* ¶¶ 621–38. Indeed, the Cochrane Collaboration considered Saito 2008, but this did not change its conclusion that omega-3-fatty acids "are probably not useful for preventing or treating CV disease." PX 953 (Abdelhamid) at 66, 74; Trial Tr. 1953:7–1954:3 (Toth Direct).

653. Finally, a person of ordinary skill would have understood that, as with Yokoyama and JELIS, Saito was not measuring EPA alone, but instead the effect of DHA and EPA because of the high fish diet of the Japanese patients studied. DX 1547 (Saito 2008) at 2; Trial Tr. 1952:8–1953:2 (Toth Re-Direct). It neither would have been understood to teach the effects of pure EPA alone, nor have motivated a person of ordinary skill to pursue high purity EPA. Trial Tr. 1952:8–1953:2 (Toth Re-Direct); *see also supra* ¶¶ 643–47.

c) WO '118 (DX 1524)

654. International Patent Application WO 2007/142118 ("WO '118") described a composition containing at least EPA or a mixture of EPA and DHA for preventing the occurrence of cardiovascular events in hypercholesterolemic patients having one or more other risk factors for cardiovascular disease. *See generally* DX 1524 (WO '118).

655. WO ’118 was not directed to patients with severe hypertriglyceridemia. DX 1524 (WO ’118) at 7; Trial Tr. 1960:1-1962:13 (Toth Re-Direct). Accordingly, it could not have provided a reasonable expectation of avoiding LDL-C increases in persons with severe hypertriglyceridemia, or in showing a cardiovascular benefit in such patients. *See supra* ¶¶ 622, 651.

656. Additionally, WO ’118 would have provided no reason to use high purity EPA over a mixture of DHA and EPA. WO ’118 preferred DHA as a fatty acid. DX 1524 (WO ’118) at 25 (“Another preferable fatty acid included is DHA-E.”); Trial Tr. 1962:14–19 (Toth Re-Direct). WO ’118 described using a formulation in which “the composition is preferably the one having a high purity of EPA-E *and* DHA-E, for example, the one having a proportion of the (EPA-E + DHA-E) in the total fatty acid and derivatives therefore preferably 40% by weight or higher.” DX 1524 (WO ’118) at 26 (emphasis added); Trial Tr. 1962:20–1963:10 (Toth Re-Direct).

657. Furthermore, WO ’118 did not distinguish EPA from DHA when discussing the effectiveness of its composition, and also noted that Omacor, *i.e.*, Lovaza, could be used in connection with the WO ’118 invention, stating that “the soft capsule Omacor™ Ross products, Reliant and Provova) containing about 46% by weight of EPA-E and about 38% by weight of DHA-E is commercially available in the U.S., Europe, and other countries as a drug applied for hypertriglyceridemia” and that “[t]hese drugs may be purchased for use in the present invention.” DX 1524 (WO ’118) at 35; Trial Tr. 1963:13–1964:2 (Toth Re-Direct). Thus, WO ’118 would have provided no motivation to deviate from LOVAZA® and use high purity EPA.

658. Defendants may also attempt to rely on the subgroup analysis of JELIS referenced in WO ’118. DX 1524 (WO ’118) at 13-14, 39. But a person of ordinary would have understood that this subgroup analysis was not in persons with severe hypertriglyceridemia, that the JELIS trial was underpowered for subgroup analysis, and that JELIS had several other design flaws. *See supra*¶¶ 621–38, 649–53.

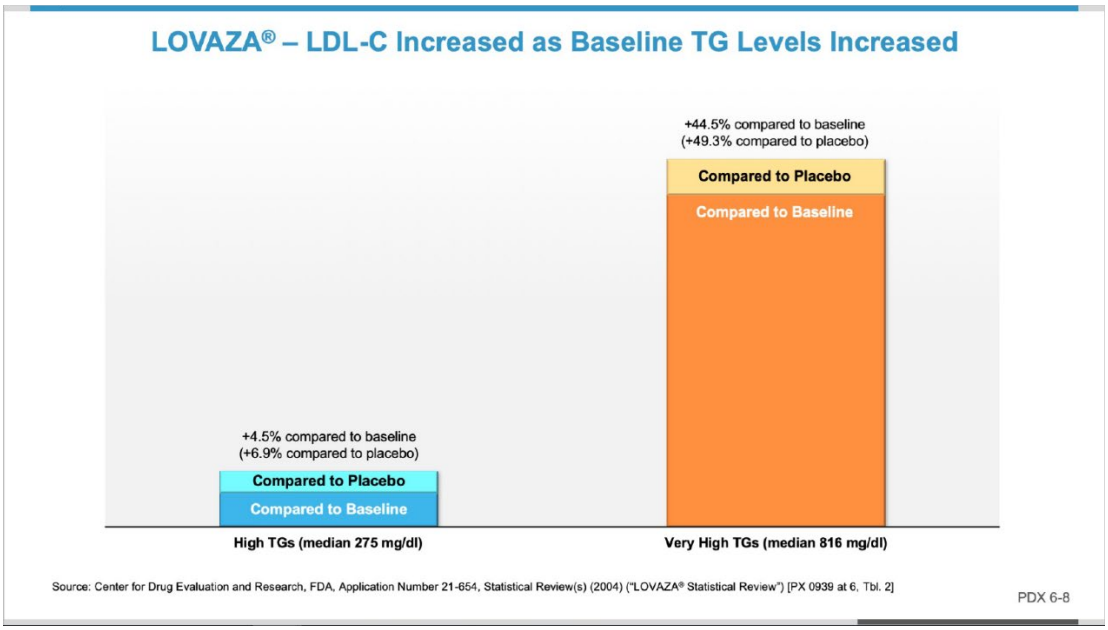
5. Other Selected Prior Art

a) Lovaza Statistical Review (PX 939)

659. The Lovaza Statistical Review summarized FDA's review of the statistical aspects of the clinical trial data submitted in support of the New Drug Application for Lovaza, which at the time of the review was known as Omacor. The Lovaza Statistical Review was finalized on October 17, 2004 and was prior art as of March 2008. *See* PX 939 (Lovaza Statistical Review) at 65; *see also* Joint Stipulations of Fact (ECF No. 324), ¶ 87. The Lovaza Statistical Review was considered by the USPTO during the prosecution of the Asserted Patents. *See* PX 21 ('728 Patent) at 4.

660. The Lovaza Statistical Review contained results from various clinical studies of Lovaza, including "Category 1" studies, which were double-blind, parallel, placebo-controlled studies or parts of studies in patients with hypertriglyceridemia or severe hypertriglyceridemia which used 4 g/day of K85 (the name of the study drug, *i.e.*, Lovaza). *See* PX 939 ("Lovaza Statistical Review"(at 5; *see also* 1588:4–1589:6 (Toth Direct). Among such studies, the U.S. studies (K85-94010 and K85-95009) examined the effect of Lovaza in patients who had TG levels of at least 500 mg/dL. *See* PX 939 (Lovaza Statistical Review) at 5; *see also* 1588:4–1589:6 (Toth Direct). On the other hand, the European studies (CK85-013, CK85-014, CK85-017, CK85-019, CK85-022, and CK85-023) involved patients with median TG levels below 500 mg/dL. *See* PX 939 (Lovaza Statistical Revew) at 5; *see also* Trial Tr. 1588:4–1589:6 (Toth Direct).

661. In the Lovaza Statistical Review, the reviewer noted that "[t]he median increase in LDL percent change from baseline was greater in the 2 U.S. studies in severe hypertriglyceridemia than in the European studies." *See* PX 939 (Lovaza Statistical Review) at 6. In the U.S. studies, whose patients had the median TG level of 816 mg/dL, LDL-C increased by 44.5% from baseline and by 49.3% compared to placebo. *See id.*, Tbl. 2. In comparison, in the European studies, whose patients had the median baseline TG level of 275 mg/dL, the patients' LDL-C increased only by 4.5% from baseline and by 6.9% compared to placebo. *See id.* These different results are summarized in PDX 6-8:



See also Trial Tr. 1634:4–15 (Toth Direct).

662. Defendants suggested, on cross-examination of Dr. Toth, that because patients in the very-high triglyceride group had a median TG level of 816 mg/dL, that a person of ordinary skill could not form an expectation about the the LDL-C effects in patients with TG levels closer to 500 mg/dL. *See* Trial Tr. 1817:16–1818:19 (Toth Cross). But the studies in the Lovaza Statistical Review did not focus on an *individual* at a specific TG level, but rather on a *patient population with severe hypertriglyceridemia*, that is, with TGs greater than or equal to 500 mg/dL. *See* PX 939 (Lovaza Statistical Review) at 4; *see also* Trial Tr. 1588:20–1589:6 (Toth Direct). Indeed, FDA defined this study group as "patients with severe hypertriglyceridemia (TG≥ 500)." PX 939 (Lovaza Statistical Review) at 4. Moreover, a person of ordinary skill would have understood from ATP-III that the different groups compared in the Lovaza Statistical Review were distinct patient populations. *See* PX 989 (ATP-III) at 194; DX 1876 (ATP-III) at 181 *see also* Trial Tr. 1569:3–24 (Toth Direct). Indeed, ATP-III—and the Lovaza Statistical Review—recognized 500 mg/dL as the cutoff for severe hypertriglyceridemia and made comparisons based on a threshold TG level of 500 mg/dL and above. *See* PX 989 (ATP-III at 194); DX 1876 (ATP-III) at 181; Trial Tr. 1569:3–24 (Toth Direct); PX 939 (Lovaza Statistical Review) at 4. And a person of ordinary skill would have adhered to the same convention. *See, e.g.*, Trial Tr. 1569:3–8 (Toth

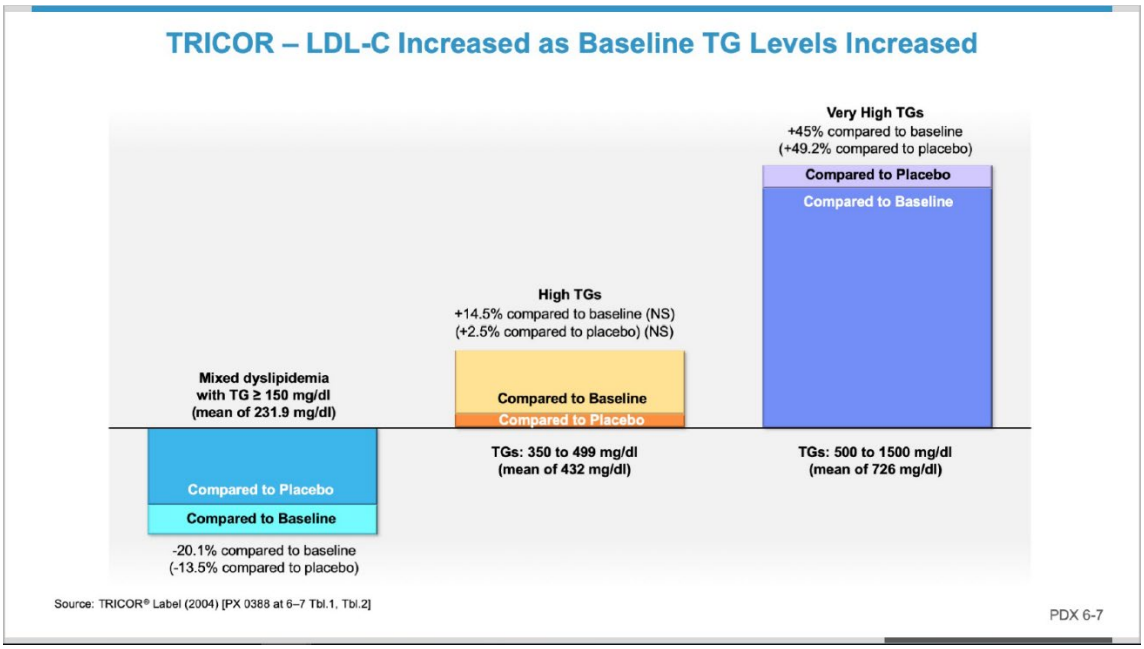
Direct). Consequently, a person of ordinary skill would have formed an expectation, based on the Lovaza Statistical Review, that patients with severe hypertriglyceridemia would have a dramatically different LDL-C response to TG-lowering treatment than patients with TGs below 500 mg/dL. *See* Trial Tr. 1587:7–1591:14 (Toth Direct).

663. The Lovaza Statistical Review also showed that Lovaza did not reduce apo B in very high TG patients. In the Lovaza Statistical Review, the apo B data for the treatment group and the placebo group were presented side-by-side in box plots as percent changes from the baseline apo B levels. *See* PX 939 (Lovaza Statistical Review) at 25, Fig. 7; *see also* Trial Tr. 1724:9–1727:13 (Toth Direct). These box plots showed that the median percent change in apo B was slightly negative for the placebo group, meaning that apo B decreased for the placebo group. *See* PX 939 (Lovaza Statistical Review) at 25, Fig. 7. In contrast, the median percent change was close to 0% for the group that received 4 g/day of K85 (Lovaza). *See id.* These data showed that apo B remained virtually unchanged compared to baseline in very high TG patients who received Lovaza, and that Lovaza *increased* apo B in those patients compared to placebo. *See id.*; *see also* Trial Tr. 1724:9–1727:13 (Toth Direct).

b) Tricor Label (PX 388)

664. The Tricor Label is the 2004 prescribing information for Tricor, the brand name for the TG-lowering agent fenofibrate. *See generally* PX 388 (Tricor Label). Tricor was FDA-approved for the treatment of severe hypertriglyceridemia. *See* PX 388 (Tricor Label) at 7.

665. As reported in the FDA-approved labeling for Tricor, and summarized in PDX 6-7 below, LDL-C responses varied greatly in patients, depending on their baseline TGs:



666. As reflected in the graph, Tricor actually *reduced* LDL-C in mixed dyslipidemic patients with merely elevated TGs. PX 388 (Tricor Label) at 6, Tbl. 1 (reporting a 14.5% reduction in LDL-C in patients with mean TG levels of 231.9 mg/dL as compared to placebo); PDX 6-7. Even in patients with high triglycerides—with baseline TGs between 350–499 mg/dL—fenofibrate only increased LDL-C a non-statistically significant ***2.5%*** compared to placebo. PX 388 (Tricor Label;) at 7, Tbl. 2; PDX 6-7. But when fenofibrate was used to treat severely hypertriglyceridemic patients—those with TGs of at least 500 mg/dL—LDL-C levels increased ***49.2%*** over placebo. PX 388 (Tricor Label;) at 7, Tbl. 2; PDX 6-7; *see also* Trial Tr. 1582:11–1584:19 (Toth Direct).

667. On cross-examination of Dr. Toth, Defendants suggested that because the mean TG level in the very-high triglyceride group was 726 mg/dL, a person of ordinary skill could not form an expectation about the the LDL-C effects in patients with TG levels closer to 500 mg/dL. *See* Trial Tr. 1819:22–1821:2 (Toth Cross). But, like Lovaza, the Tricor label did not focus on an *individual* at a specific TG level, but rather a *population with severe hypertriglyceridemia*, with TGs greater than or equal to 500 mg/dL, and compared that to: (1) a population with TGs between 350 and 499 mg/dL, and (2) another population with mixed dyslipidemia (mean TG of 231.9)

mg/dL. *See* PX 388 (Tricor Label) at 6–7; *see also* Trial Tr. 1582:15–1584:19 (Toth Direct). A person of ordinary skill would have understood from ATP-III that these were distinct patient populations. *See* PX 989 (ATP-III) at 194; DX 1876 (ATP-III) at 181; *see also* Trial Tr. 1569:3–24 (Toth Direct). Indeed, ATP-III—and the Tricor label—recognized 500 mg/dL as the cutoff for severe hypertriglyceridemia and made comparisons based on TG levels of 500 and above. *See* PX 989 (ATP-III) at 194; DX 1876 (ATP-III) at 181; Trial Tr. 1569:3–24 (Toth Direct); PX 388 (Tricor Label) at 6–7. And a person of ordinary skill would have adhered to the same convention. *See, e.g.*, Trial Tr. 1569:3–8 (Toth Direct). A person of ordinary skill therefore would have understood from the Tricor Label that patients with severe hypertriglyceridemia have a dramatically different LDL-C response to TG-lowering treatment than patients with TGs below 500 mg/dL. *See* Trial Tr. 1584:8–23 (Toth Direct) ("But then when you go above 500 you zoom up.").

G. Defendants' Have Failed to Adduce Clear and Convincing Evidence That a Person of Ordinary Skill in March 2008 Would Have Been Motivated to Use Purified EPA to Treat Severe Hypertriglyceridemia

668. Defendants have not demonstrated by clear and convincing evidence that a person of ordinary skill would have been motivated to use high purity EPA to treat severe hypertriglyceridemia, a critical element of establishing obviousness. Trial Tr. 1639:3–1703:7 (Toth Direct). Defendants contend that a person of ordinary skill in March 2008 would have been motivated to eliminate DHA from Lovaza—which contains a mixture of EPA and DHA (and other naturally occurring omega-3 fatty acids)—and instead use a high purity EPA treatment for severe hypertriglyceridemia. But nothing in the prior art, including Defendants' "key prior art," would have motivated a person of ordinary skill to do so. To the contrary, the prior art, including the very Mori 2000 reference upon which Defendants rely, expressly taught that *DHA* was the superior therapeutic agent. *See supra* ¶¶ 549–63. Thus, if a person of ordinary skill in the art had set out to make an improved omega-3 fatty acid formulation for treatment of severe hypertriglyceridemia, that person would not have eliminated DHA from Lovaza or otherwise arrived at a high purity EPA formulation.

669. Nothing in any of the four references in Defendants' proposed combination would have motivated a person of ordinary skill to use 4 g of high purity EPA to treat patients with severe hypertriglyceridemia.

670. The Lovaza PDR (DX 1535) would not have motivated a person of ordinary skill to eliminate substantially all of the DHA and instead use only high purity EPA to treat severe hypertriglyceridemia. Trial Tr. 1677:5–23 (Toth Direct). Nothing in the Lovaza PDR suggested that it would be advantageous to use high purity EPA instead of an EPA-DHA mixture, nor did the Lovaza PDR draw any comparisons between the individual effects of DHA and EPA. *See generally* DX 1535 (Lovaza PDR); Trial Tr. 1677:13–18 (Toth Direct).

671. Moreover, while Defendants contend that it was "possible to counteract the LDL-C increases that were seen with Lovaza using statins," Trial Tr. 809:21–810:2 (Heinecke Direct), the reason they offer for why a person of ordinary skill would have wanted to modify Lovaza is to avoid the need to co-administer a statin and the attendant patient compliance issues stemming from having to take two pills instead of one. *See* Trial Tr. 813:8–19 (Heinecke Direct) ("Q: Even though LDL-C could be reduced with statins, was there still a motivation to improve Lovaza to avoid increases in LDL-C? A: Yes, there is. Obviously patient compliance is a major issue in clinical medicine. For example, most patients prescribed statins don't take them after six months. . . . It's clearly easier to take one pill, for example, of pure EPA to treat a condition than to combine two pills such as Lovaza with a statin."). But Defendants offered no explanation as to why the person of ordinary skill in the art would not have simply placed Lovaza and the statin in a single dosage form. Nor could they have done so. As Dr. Fisher readily admitted, "it's possible to take two active ingredients and put it in one drug product." Trial Tr. 1164:2–4 (Fisher Cross). Accordingly, there would have been no reason to pursue high purity EPA, or to change Lovaza.

672. Nor would Hayashi (DX 1532) or Kurabayashi (DX 1534) have motivated a person of ordinary skill to substitute highly purified EPA for the Lovaza composition. Trial Tr. 1677:24–1679:1 (Toth Direct). Neither of these references taught that one could avoid substantial increases in LDL-C in persons with severe hypertriglyceridemia by administering highly purified EPA, nor

did they provide a reasonable expectation of success in doing so. *See supra* ¶¶ 564–82. Neither of these publications studied lipid effects of purified EPA in populations with very high triglycerides, and Kurabayashi did not look at the effect of EPA alone in any population, but instead studied the effects of EPA in conjunction with estriol. *See supra* ¶¶ 564–82. Neither of these references state that high purity EPA had advantages over DHA. DX 1532 (Hayashi); DX 1534 (Kurabayashi); Trial Tr. 1677:24–1679:1 (Toth Direct).

673. Nor would Mori 2000 (DX 1538) have motivated a person of ordinary skill to eliminate DHA from Lovaza, as Mori taught that *DHA* was the superior therapeutic agent. *See supra* ¶¶ 549–63; *see also* DX 1538 (Mori 2000) at 4 ("We found that DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL2-cholesterol subfraction without adverse effects on fasting glucose concentrations."); Trial Tr. 1645:16–1646:17 (Toth Direct). Indeed, Mori 2000 taught that DHA was *at least as good* as EPA at lowering triglycerides, and that it had several *advantages* in terms of cardiovascular health—on HDL-C, LDL particle size, and fasting glucose. *See supra* ¶¶ 553–63. Thus, far from motivating a person of ordinary skill to *eliminate* DHA, Mori 2000 would have led a person of ordinary skill in the art to keep it.

674. Mori 2000 taught away from using high purity EPA in patients with severe hypertriglyceridemia, as it disclosed that only EPA increased fasting glucose. *See* DX 1538 (Mori 2000) at 8; *see also* Trial Tr. 1647:20–1648:13 (Toth Direct); *see also supra* ¶¶ 562–63. In March 2008, a person of ordinary skill in the art would have understood that an increase in fasting glucose "could be a manifestation of insulin resistance[]"; "have adverse effects on arterial walls[]"; and "also contribute to the development of atherosclerotic disease. . . ." Trial Tr. 1648:3–1648:13 (Toth Direct). Moreover, an increase in fasting glucose would be of particular concern to patients with diabetes, who make up a "good percentage" of patients with severe hypertriglyceridemia. *See* Trial Tr. 1648:18–1649:12 (Toth Direct). On cross-examination, Dr. Heinecke also acknowledged that fasting glucose was an important cardiovascular risk factor for diabetics; that many patients with severe hypertriglyceridemia have diabetes; and that a person of ordinary skill would not have

wanted to develop a treatment for severe hypertriglyceridemia that harmed diabetic patients. Trial Tr. 903:25–904:9 (Heinecke Cross).

675. Mori's observation that DHA has advantages over EPA was echoed in other prior art as of March 2008, further confirming that a person of ordinary skill would not have wanted to eliminate DHA from the Lovaza treatment, or otherwise use only high purity EPA. Trial Tr. 1679:2–1703:7 (Toth Direct). As with Mori 2000, for example, other prior reported that DHA raised HDL-C, the so-called "good cholesterol." *See* PX 918/DX 1933 (Agren) at 6 ("Sanders and Hinds found increased HDL and HDL_2 cholesterol concentrations after DHA-rich fish oil intake and proposed that DHA is responsible for these changes. The greatest increase in the DHA oil group in the present study supports this idea."); Trial Tr. 1682:20–1683:25 (Toth Direct).

676. Other prior art also disclosed, as Mori 2000 did, that DHA increased LDL-C particle size—an effect that Mori recognized could help lower atherogenic risk. DX 1538 (Mori 2000) at 6 ("LDL particle size increased significantly with DHA supplementation, a result that might be expected to contribute to a reduction in atherogenic risk."); Trial Tr. 1684:1–1686:3 (Toth Direct). For example, in a 2003 article, Drs. Woodman and Mori reported that "LDL particle size increased after supplementation with DHA but not EPA." PX 563 (Woodman) at 1. The authors proceeded to report that supplementation with purified DHA increases LDL particle size, reduces serum triglycerides, increases HDL_2 cholesterol, and improves vascular function and blood pressure. *Id.* The authors further concluded that, "for subjects with type 2 diabetes, DHA may have more therapeutic value than EPA as a food additive." *Id.* This would have been viewed as important for patients with very high TGs, because many such patients have diabetes. Trial Tr. 904:4–6 (Heinecke Cross).

677. The prior also reported that DHA had advantages over EPA in terms of blood pressure. Trial Tr. 1685:12–1689:12 (Toth Direct). Because high blood pressure was associated with increased risk of cardiovascular disease, a person of ordinary skill in March 2008 would have understood that an agent that was more effective in lowering blood pressure was desirable. Trial Tr. 1686:4–19 (Toth Direct).

678. For example, a 1999 paper by Dr. Mori reported that "purified DHA but not EPA reduced ambulatory BP [(blood pressure)] and HR [(heart rate)] in mildly hyperlipidemic men" and that "[t]he results … suggest that DHA is the principal omega-3 fatty acid in fish and fish oils . . . responsible for their BP- and HR-lowering effects in humans." PX 565 (Mori 1999) at 2.

679. Similarly, a 1996 reference by McLennan reported that DHA had an advantage over EPA in terms of blood pressure, PX 386 (McLennan); Trial Tr. 1688:4–1689:12 (Toth Direct). Discussing the relative effects of EPA and DHA on blood pressure, the authors observed that "there was a clear order of blood pressure retardation between the diets (docosahexaenoic acid diet > eicosapentaenoic acid + docosahexaenoic acid diet > eicosapentaenoic acid diet)" and that "the presence of docosahexaenoic acid seemed to be most important, with eicosapentaenoic acid providing some effect if present in high enough concentrations." *See* PX 386 (McLennan) at 6; *see also* Trial Tr. 1689:1–12 (Toth Direct). The authors further concluded "that DHA may be the principal active component conferring cardiovascular protection." PX 386 (McLennan) at 1; Trial Tr. 1688:20–25 (Toth Direct).

680. In evaluating the overall profiles of DHA and EPA, a person of ordinary skill in the art would have taken all of these advantages of DHA into account. Trial Tr. 1689:19–1690:10 (Toth Direct). Taken together, these factors would have led a person of ordinary skill to retain substantial amounts of DHA in any omega-3 fatty acid formulation. Trial Tr. 1689:19–1690:10 (Toth Direct). A person of ordinary skill in the art would not have focused solely on LDL-C, as these other factors were also understood to affect cardiovascular risk. Trial Tr. 1689:19–1690:25 (Toth Direct).

681. A person of ordinary skill would not have believed that EPA would offer any advantage over DHA in patients with severe hypertriglyceridemia. A person of ordinary skill in the art would have understood that *both* DHA and EPA would greatly increase LDL-C in patients with severe hypertriglyceridemia, simply as a function of how omega-3 formulations were understood to lower TGs—by converting VLDL to LDL. *See supra* ¶¶ 39–53, 548, 550–52.

Furthermore, even in persons with TGs below 500 mg/dL, the prior art did not teach that EPA offered an advantage over DHA with respect to LDL-C. Trial Tr. 1690:11–1700:7 (Toth Direct).

682. Defendants contend that because the LDL-C increase of 3.5% observed in the EPA arm in Mori 2000 was not statistically significant, and the LDL-C increase of 8% in the DHA arm was statistically significant, the person of ordinary skill would have concluded that DHA, but not EPA, raised LDL-C levels. This argument is flawed for multiple reasons.

683. First, Mori 2000 addressed the different effects of DHA and EPA in patients who are *mildly* hyperlipidemic—the mean baseline TG level in the study was less than 200 mg/dL—not *severely* hypertriglyceridemic. DX 1538 (Mori 2000) at 1, 4; Trial Tr. 1640:10–1643:19 (Toth Direct). For this reason, Mori 2000 would not have erased what was understood to be the mechanism by which triglycerides are lowered in severely hypertriglyceridemic patients—the conversion of VLDL to LDL—let alone the prior experience with niacin, fibrates, and Lovaza. *See supra* ¶¶ 39–53, 548, 550–52. The person of ordinary skill would have expected that both DHA and EPA would dramatically raise LDL-C in patients with severe hypertriglyceridemia, *see* Trial Tr. 1642:14–1643:19, 1665:17–1669:16 (Toth Direct), and thus would have understood that EPA conferred no advantage over DHA with respect to LDL-C, without regard to Mori 2000.

684. Additionally, even in patients with TGs below 500 mg/dL, the prior art as a whole reported that EPA raised LDL-C. Trial Tr. 1690:21–1700:7 (Toth Direct). For example, a prior art study by Rambjør investigating whether EPA, DHA, or both were responsible for the TG-lowering effects of fish oil reported that study subjects receiving EPA, LDL-C increased in a statistically significant way from 2.81 millimoles per liter to 2.97 millimoles per liter. DX 1961 (Rambjør) at 3, 5, Tbl 3; Trial Tr. 1691:12–1692:19 (Toth Direct). The sample size of patients receiving EPA was 25—which exceeded the sample size of the 19 subjects who received EPA in Mori. DX 1961 (Rambjør) at 5, Tbl. 3; Trial Tr. 1692:20–25 (Toth Direct); *see also supra* ¶¶ 595–97. While Dr. Heinecke testified that a person of ordinary skill would have disregarded Rambjør after the Mori paper was published in 2000 (Trial Tr. 784:6-785:2) that contention is belied by publications after

Mori 2000 that continued to cite Rambjør. PX 909 (Geppert) at 8 (citing Rambjør); DX 1605 (von Schacky) at 9, Tbl. 1.

685. Furthermore, far from consistently reporting that DHA raised LDL-C in patients with TGs below 500 mg/dl, some prior art reported that DHA did not raise LDL-C. Trial Tr. 1693:5–1695:11 (Toth Direct); DX 1933 (Agren) at 8, Tbl. 3 ("No tendency to increased LDL cholesterol was seen in the DHA-oil group in the present study."); DX 1949 (Conquer) at 4 ("[N]o significant alteration was found in the total and LDL-cholesterol levels with DHA supplementation. . . ."); *see also* Trial Tr. 1187:15–19 (Fisher Cross) ("Q. There were publications that actually [said] that DHA may lower LDL more, correct?" A. That's correct.").

686. To be sure, there was inconsistency in the reported LDL-C outcomes for DHA and EPA in persons with normal to high triglyceride levels, which the prior art noted. Trial Tr. 1695:12–1697:19 (Toth Direct). For example, Hayashi observed that "[d]ata on the effects of fish oils rich in N-3 fatty acids on plasma low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were contradictory in some cases." DX 1532 (Hayashi) at 3. And a prior art reference by Geppert noted that "[i]nconsistent effects of DHA on LDL cholesterol levels were reported in previous studies; some investigators found a LDL cholesterol-raising effect of DHA or no effect on LDL cholesterol levels.") PX 909 (Geppert) at 8. But the inconsistency in reported LDL-C outcomes with DHA and EPA is further reason that it was not known or reasonably expected that EPA had an LDL-C advantage over DHA—or that DHA, but not EPA, raised LDL-C—in *any* patient population.

687. Even if the person of ordinary skill had looked only at Mori 2000 in isolation, moreover, that person would not have read it as teaching that DHA but not EPA increased LDL-C in the population studied. That person would have attributed the reported 4.5% difference in LDL-C between DHA and EPA to the different baseline TGs in the DHA and EPA groups: the subjects in the EPA arm had a mean TG level more than 10% lower than the DHA group, which could explain the smaller increase in LDL-C with EPA (since LDL-C increases were understood to increase as baseline TGs increased). Trial Tr. 1643:3–1644:11 (Toth Direct); Trial Tr. 1579:1–

18 (Toth Direct); *see also supra* ¶¶ 550–52. The person of ordinary skill would have understood additionally that the LDL-C increase in the EPA arm was not statistically significant because of the small sample size—only 19 subjects. Trial Tr. 1643:20–1644:11 (Toth Direct). Indeed, in just a slightly larger sample of 25 subjects, Rambjør reported that EPA *did* increase LDL-C, even in persons with TGs below 500 mg/dL. *See supra* ¶¶ 550–52, 596.

688. On balance, the prior art as a whole reported that both EPA and DHA raised LDL-C—even in patients with TG levels below 500 mg/dL. Trial Tr. 1697:16–1700:7 (Toth Direct). This was evident from the a 2006 review publication by von Schacky (DX 1605), which surveyed the literature and drew conclusions about the relative effects of EPA and DHA on lipid effects and other parameters including LDL-C, based on a wide range of sources. DX 1605 (von Schacky); Trial Tr. 1697:16–1700:7 (Toth Direct).; *see also supra* ¶¶ 606–11.

689. In the von Schacky article, the author conducted an extensive review of the literature, conducting various Medline searches, examining the Cochrane Review database, and consulting articles maintained in his personal database that had been generated over more than 20 years. DX 1605 (von Schacky) at 2; Trial Tr. 1945:24–1946:16 (Toth Re-Direct). After conducting this review, the author summarized the effects of purified EPA and DHA as observed in human studies on a variety of risk factors for cardiovascular disease, reporting semi-quantitative conclusions from the literature. DX 1605 (von Schacky) at 9, Tbl. 1; Trial Tr. 1698:2–1703:7 (Toth Direct). The table reporting these conclusions appears immediately below:

Table 1 Effects of purified eicosapentaenoic and docosahexaenoic acid, as observed in human studies, only significant differences were considered for inclusion. Arrows reflect semi-quantitatively the findings from the literature

	EPA	DHA
Triglycerides	↓↓	↓↓
Cholesterol	↔	↔
LDL	↑	↑
HDL	↔?	↑?
platelet aggregability	(↓)	↓
mean platelet volume	↓	↔
blood pressure	↔	↓
heart rate	↓	↓↓
endothelial function	↔	↑
glucose metabolism	↔	↔

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Note: Information sourced from von Schacky and Weber 1985; Nozaki et al 1992; Rambjor et al 1996; Grimsgaard et al 1997, 1998; Mori, Bao, et al 1999; Mori, Burke, et al 2000; Mori, Watts, et al 2000; Woodman et al 2000, 2002, 2003a, 2003b; Park and Harris 2002; Mori and Woodman 2006.

690. At the bottom of the table under "note," von Schacky identified 14 manuscripts as the source for the information in the table—including the Mori 2000 reference and the Rambjør paper. DX 1605 (von Schacky), at 9, Tbl. 1; Trial Tr. 1699:10–1700:7 (Toth Direct). In the table itself, von Schacky reported that DHA and EPA were understood to have the same relative effects on LDL-C—with both EPA and DHA receiving a single upward arrow, meaning that on balance both EPA and DHA raised LDL-C, and to the same degree. DX 1605 (von Schacky) at 9; Trial Tr. 1699:15–1700:20 (Toth Direct).[18]

[18] Defendants also attempt to bolster their position that DHA but not EPA was understood to raise LDL-C in patients with TGs below 500 mg/dL by looking at a 2011 article discussing the MARINE study. DX 1741 (Bays 2011). Defendants focus on a statement that "in several small studies" "DHA treatment generally increased LDL cholesterol levels, [while] EPA did not." DX 1741 (Bays 2011) at 7. But this article from 2011 was not prior art—and therefore would not have been available to a person of ordinary skill in the art—and its conclusions were informed in large part by events and publications after March 2008. DX 1741 (Bays 2011) at 7, 9; Trial Tr. 1954:4–1956:12 (Toth Re-Direct). Moreover, all of the studies referenced in the publication were small, and none were in persons with severe hypertriglyceridemia—which the article specifically notes. DX 1741 (Bays 2011) at 7, 9; Trial Tr. 1956:13–1957:9 (Toth Re-Direct). And the article went on

691. Defendants point to a statement in the text of von Schacky stating that in Mori 2000 "no effects of either EPA or DHA" were seen on LDL-C. DX 1605 (von Schacky) at 5. But elsewhere in the article, under a heading discussing DHA and EPA, von Schacky reported that "[r]ather consistently, LDL has been seen to be increased with a few exceptions" with both DHA and EPA, thereby strongly supporting the conclusions in Table 1 that, on the whole, both EPA and DHA were understood to raise LDL-C. DX-1605 (von Schacky) at 4–5; Trial Tr. 1947:3–1948:21 (Toth Re-Direct).

692. The table also reported that *DHA* had advantages over EPA with respect to several other parameters—HDL effects, blood pressure, heart rate, and endothelial function. DX 1605 (von Schacky) at 9, Tbl. 1; Trial Tr. 1700:8–1703:7 (Toth Direct). For *no factor* was EPA reported to offer an advantage over DHA. DX 1605 (von Schacky) at 9, Tbl. 1; Trial Tr. 1702:19–1703:7 (Toth Direct).

693. Dr. Heinecke attempted to belittle von Schacky as a "review" with "no primary data" in the paper. Trial Tr. 785:3–12 (Heinecke Direct). But as both Drs. Heinecke and Toth agreed, this publication was a synthesis "of what the literature showed" about the relative effects of DHA and EPA. Trial Tr. 785:3–12 (Heinecke Direct); Trial Tr. 1698:2–16 (Toth Direct). It is therefore entitled to a great deal of weight in determining how the person of ordinary skill, reviewing the art as a whole, would have assessed the comparative attributes of DHA and EPA.

694. Defendants attempted to discredit the von Schacky reference on the ground that its conclusions were semi-quantitative, and that the arrows showing directional effects of DHA and EPA were supposedly "totally unclear." Trial Tr. 785:13–786:14 (Heinecke). But a person of ordinary skill would have found a semi-quantitative evaluation helpful because one can tell quickly by looking, based on the number and direction of arrows, how DHA and EPA compare on a variety of effects. Trial Tr. 1701:12–22 (Toth Direct). And when a person of ordinary skill looks at the comparison, it is clear that EPA was not understood to have *any* advantages over DHA, and that

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to note that an "unexpected finding was that Vascepa produced no significant increase in LDL cholesterol levels" in patients with severe hypertriglyceridemia. DX 1741 (Bays 2011) at 7.

DHA was understood to have *several* advantages over EPA. Trial Tr. 1702:19–1703:7 (Toth Direct); DX 1605 (von Schacky) at 9, Tbl. 1.

695. Von Schacky thus underscores that a person of ordinary skill would not have been led to eliminate DHA from Lovaza, given all of the advantages observed with DHA, and the absence of any advantage for EPA. Trial Tr. 1702:19–1703:7 (Toth Direct). A person of ordinary skill would have believed that eliminating DHA from Lovaza would make Lovaza *worse*—which a POSA would not have wanted to do. Trial Tr. 1948:16–1949:1 (Toth Re-Direct).

696. That none of Defendants' references, including the "key prior art," would have motivated a person of ordinary skill to eliminate DHA from Lovaza is reinforced by testimony from Defendants' expert Dr. Fisher. Dr. Fisher testified that when Lovaza was approved in 2004—after Mori 2000 (DX 1538), Hayashi 1995 (DX 1532), and Kurabyashi 2000 (DX 1534)—neither he nor any of his colleagues at the National Lipid Associated believed that the makers of Lovaza "gotta get this DHA out of there." Trial Tr. 1187:4–14 (Fisher Cross). Moreover, Dr. Fisher testified that even when VASCEPA was launched, people were not immediately switching from the predominantly DHA-EPA mixture of Lovaza to the high purity EPA treatment of Lovaza—thus indicating that it was not obvious that high purity EPA had advantages over the Lovaza mixture. Trial Tr. 1186:14–1188:4 (Fisher Cross).

697. Nothing about the JELIS trial would have motivated a person of ordinary skill in the art to use high purity EPA for the treatment of severe hypertriglyceridemia. As noted above, JELIS did not concern patients with severe hypertriglyceridemia, but instead hypercholesterolemic patients with TG levels that were only slightly above normal—with a mean TG level of 153 mg/dL. DX 1553 (Yokoyama 2007) at 3, Tbl. 1; Trial Tr. 1744:18–1745:21 (Toth Direct). JELIS therefore taught nothing about the LDL-C effects of a TG-lowering agent in patients with severe hypertriglyceridemia, and would not have provided a reasonable expectation of avoiding LDL-C increases if administering EPA to patients with severe hypertriglyceridemia. *See supra*¶¶ 39–53, 622.

698. Nor would JELIS have provided any expectation that high purity EPA would reduce cardiovascular risk in patients with severe hypertriglyceridemia. Even in patients with lower baseline TG levels, JELIS was not widely accepted as establishing cardiovascular benefit. *See supra* ¶¶ 621–38. Because of its many methodological flaws, the person of ordinary skill in the art in March 2008 would certainly not have taken its 19% cardiovascular risk reduction at face value. *See supra* ¶¶ 621–38.

699. But even if one had taken at face value the reported 19% risk reduction in the primary endpoint, JELIS still would not have provided any basis to expect that high purity EPA would reduce cardiovascular risk in severely hypertriglyceridemic patients. In that patient population, a person of ordinary skill would have expected to see large LDL-C increases from a TG-lowering agent—including EPA—which would have negated any cardiovascular benefits reported in patients with lower TG levels. *See supra* ¶¶ 39–53, 622.

700. If JELIS had motivated a person of ordinary skill to pursue an omega-3 fatty acid formulation, it would not have been high purity EPA, but instead one with substantial amounts of DHA. *See supra* ¶¶ 643–45. The JELIS trial was administered exclusively to Japanese subjects, whose diet is very high in fish consumption—approximately 5 times higher than in other countries according to Yokoyama. DX 1553 (Yokoyama 2007) at 7; Trial Tr. 1763:4-1764:16 (Toth Direct). Because fish contain natural amounts of DHA, the high fish intake in Japanese persons meant that Japanese subjects in Yokoyama ingested large amounts of DHA through diet alone. Trial Tr. 1763:4–1764:16 (Toth Direct); Trial Tr. 1969:3–8 (Toth Re-Direct); Trial Tr. 1152:23–1153:13 (Fisher Cross).

701. Thus, if a person of ordinary skill had sought to pursue a formulation that mimicked in a Western population the composition of the omega-3 fatty acids that JELIS subjects consumed through diet and medication, that person would have included substantial amounts of DHA. Trial Tr. 1763:1–1764:16 (Toth Direct); Trial Tr. 1969:3–8 (Toth Re-Direct). That a person of ordinary skill in the art would have wanted to pursue a fatty acid formulation with substantial amounts of DHA is further reinforced by the fact that the prior art taught several *advantages* with DHA over

EPA, *see supra* ¶¶ 553–63, 604, 608–10, 673–81, and reflected in the fact that all ongoing cardiovascular outcome trials under way as of March 2008 included formulations containing substantial amounts of DHA. *See supra* ¶¶ 142–51.

702. Dr. Heinecke's testimony confirms that a person of ordinary skill would not have been motivated to use high purity EPA in patients with severe hypertriglyceridemia. *See* Trial Tr. 849:21–850:13 (Heinecke Cross) ("So, in my opinion, I'm— I don't think this is a major issue. You're not going to be using EPA to lower triglycerides above 500 in order to reduce cardiovascular risk. That's not what any clinician would do.").

703. Additionally, following JELIS, Dr. Fisher did not recommend using high purity EPA for to address cardiovascular risk for any population. *See supra* ¶¶ 634–35.

H. Defendants' Have Failed to Adduce Clear and Convincing Evidence That a POSA in March 2008 Would Have Had a Reasonable Expectation of Success That Purified EPA Would Reduce TGs in SHT Patients without Raising LDL-C

704. Defendants concede that the prior art did not teach the effect of purified EPA on the LDL-C levels of patients with severe hypertriglyceridemia. *See* Trial Tr. 800:2–5 (Heinecke Direct) ("And so I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter."); *see also* Trial Tr. 798:23–799:11 (Heinecke Direct) ("I'm not arguing here that we know what the impact is of EPA on LDL cholesterol levels above 500 milligrams per deciliter"); Trial Tr. 832:8–20 (Heinecke Cross) ("Q. So in terms of the key prior art, there's no description of the effect of pure EPA on patients with severe hypertriglyceridemia. A. I think there is evidence that EPA would lower triglycerides in patients with high triglycerides above 500, *but there was no direct evidence on LDL cholesterol.*") (emphasis added).

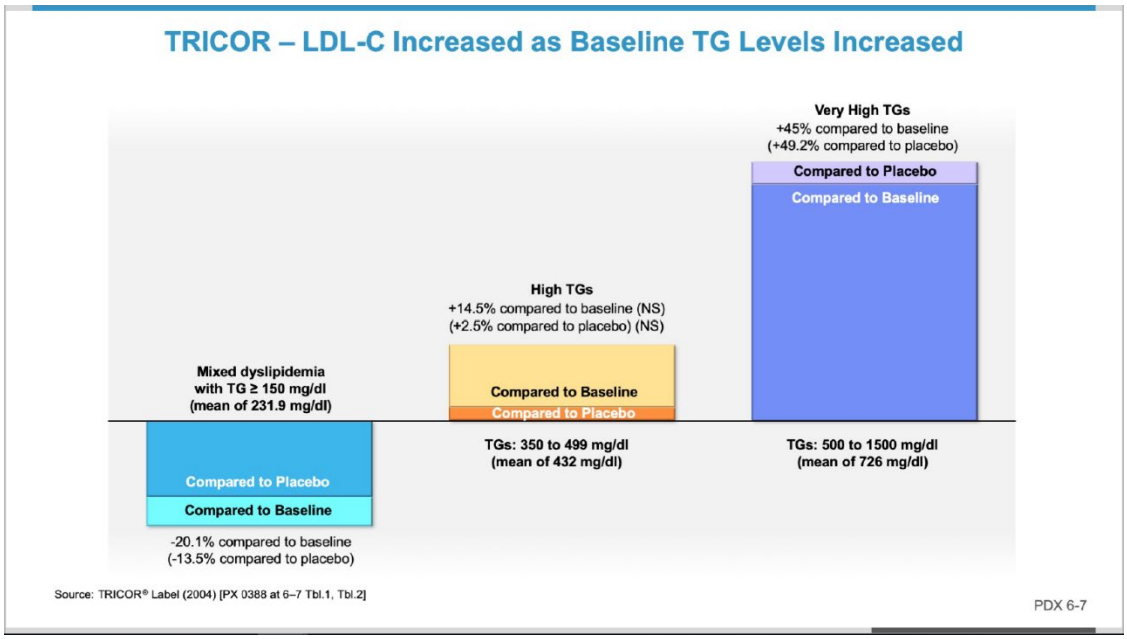
705. Defendants' contention that a person of ordinary skill in the art would have reasonably expected success in avoiding LDL-C increases in patients with severe hypertriglyceridemia rests on the erroneous assertion that a person of ordinary skill in the art would have expected that LDL-C levels in patients with severe hypertriglyceridemia would respond in

the same way as patients with only moderately elevated TGs. Trial Tr. 788:25–789:14 (Heinecke Direct). Defendants' expert testified that "typically, if one observes [an] effect on a value at a lower level, one anticipates seeing a similar effect a higher levels of that value." *Id.*

706. But there is no reason why the person of ordinary skill would have relied on what may *typically* be the case when the prior art taught what the effect had been *specifically* when TG-lowering agents had been administered to patients with severe hypertriglyceridemia. Without exception, the prior art taught that in that specific context the effect of TG-lowering agents on LDL-C depended upon the baseline TG levels of the patient population, and that severely hypertriglyceridemic patients experienced large LDL-C increases even when persons with lower TGs did not. *See supra* ¶¶ 33–34, 39–53; *see also* Trial Tr. 1667:11–1668:7 (Toth Direct).

707. A person of ordinary skill in the art understood from fibrates, for example, that LDL-C increased dramatically when reducing TGs in patients with severe hypertriglyceridemia, even though fibrates reduced LDL-C in patients with moderately elevated TGs. *See supra* ¶¶ 39–53, 664–67.

708. As noted above, the TG-lowering agent fenofibrate (marketed under the brand name Tricor) actually *reduced* LDL-C in mixed dyslipidemic patients with merely elevated TGs. PX 388 (Tricor Label) at 6, Tbl. 1 (reporting a 14.5% reduction in LDL-C in patients with mean TG levels of 231.9 mg/dL as compared to placebo); PDX 6-7. Even in patients with high triglycerides—with baseline TGs between 350–499 mg/dL—fenofibrate only increased LDL-C a non-statistically significant ***2.5%*** compared to placebo. PX 388 (Tricor Label) at 7, Tbl. 2; PDX 6-7. But when fenofibrate was used to treat severely hypertriglyceridemic patients—those with TGs of at least 500 mg/dL—LDL-C levels increased ***49.2%*** over placebo. PX 388 (Tricor Label) at 7, Tbl. 2; PDX 6-7; *see also* Trial Tr. 1582:11–1584:19 (Toth Direct). These differential effects are illustrated below in PDX 6-7:



709. Goodman & Gilman's *Pharmacologic Basis of Therapeutics*, a standard reference, observed that:

> In patients with mild hypertriglyceridemia (e.g., triglycerides <400 mg/dl), fibrate treatment decreases triglyceride levels by up to 50% and increases HDL-C concentrations about 15%; LDL-C levels may be unchanged or increase. The second-generation agents, such as fenofibrate, bezafibrate, and ciprofibrate, lower VLDL levels to a degree similar to that produced by gemfibrozil, but they also are more likely to decrease LDL levels by 15% to 20%. In patients with more marked hypertriglyceridemia (e.g., 400 to 1000 mg/dl), a similar fall in triglycerides occurs, but LDL increases of 10% to 30% are seen frequently.

PX 1027 (Goodman & Gilman 2006) at 31 (emphasis added); Trial Tr. 1584:20–1586:24 (Toth Direct).

710. A person of ordinary skill in the art would have understood in 2008 that omega-3-fatty acids, including EPA and DHA, worked like fibrates in reducing TGs in patients with severe hypertriglyceridemia. Trial Tr. 1589:15–1597:13 (Toth Direct). For example, a prior art reference by Bays entitled *Prescription Omega-3 Fatty Acids* explained as follows:

> ***As with fibrates***, the degree of LDL-C elevations observed with omega-3 treatment is generally related to the pretreatment triglyceride levels. Omega-3 fatty acids increase LDL cholesterol levels the most in patients with the highest pretreatment triglyceride

> levels. ***The reason for the increased LDL cholesterol levels with omega-3 fatty acids is related to the increased conversion of VLDL particles to LDL particles."***

PX 486 (Bays 2008) at 10, 12 (emphasis added); *see also* Trial Tr. 1596:11–1597:13 (Toth Direct).

711. Other prior art echoed that view that omega-3 fatty acids worked like fibrates in reducing TGs in patients with severe hypertriglyceridemia. For example, the 2007 McKenney reference reported:

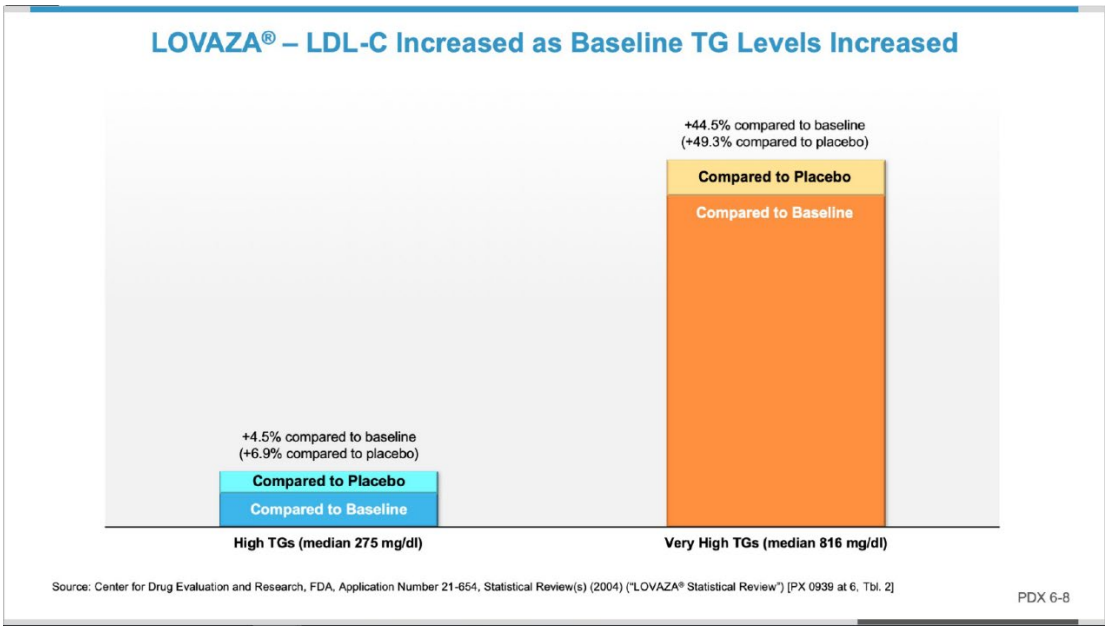
> The triglyceride reducing effects of EPA and DHA have been detailed in numerous studies among a wide range of patient types. . . . ***As with fibric acid derivatives (fibrates) and nicotinic acid derivatives (niacin)***, reductions in triglycerides and very-low-density-lipoprotein (VLDL) cholesterol are generally greater in patients with higher baseline triglyceride levels. ***An increase in low-density-lipoprotein (LDL)*** and high-density-lipoprotein (HDL) cholesterol c***an accompany a reduction in triglycerides***; ***the higher the baseline triglyceride level, the greater these lipids may be increased***.").

PX 923 (McKenney I) at 5 (emphasis added).

712. McKenney went on to observe that, under the influence of omega-3 fatty acids, "the conversion of VLDL to LDL particles increased 93 percent"—showing that with omega-3 fatty acids "VLDL particles are rapidly converted to LDL particles, *thus explaining why LDL cholesterol levels may rise in patients with very high triglycerides when given P-O3FA therapy*." PX 923 (McKenney I) at 5 (emphasis added); Trial Tr. 1593:16–1595:3 (Toth Direct).

713. Even Dr. Heinecke admitted on cross-examination that prior art suggested that fibrates and omega-3 fatty acids had the same mechanism of action in lowering TGs: fibrates, like omega-3 fatty acids, work by enhancing the conversion of TG-rich VLDL particles to LDL. Trial Tr. 884:2–886:10 (Heinecke Cross); PX 1027 (Goodman & Gilman 2006) at 30. Indeed, Dr. Heinecke admitted that in 2004 *FDA* stated that the mechanism by which one fibrate, fenofibrate, lowered TGs was the enhanced clearance of VLDL to LDL-C. Trial Tr. 880:19–883:1 (Heinecke Cross); PX 388 (Tricor Label) at 2.

714. Moreover, as with fibrates, omega-3 fatty acids had shown differential effects on LDL-C depending on baseline TGs. As with fibrates, clinical studies with Lovaza reported LDL-C increases of approximately 45–50% in patients with TGs of at least 500 mg/dL. PX 939 (Lovaza Statistical Review) at 5–6; PDX 6-8; Trial Tr. 1587:4–1590:11 (Toth Direct). These increases were observed in patients with very high TGs notwithstanding the fact that Lovaza increased LDL-C much more modestly—by only approximately ***4.5–7%***—in patients with lower TG levels. PX 939 (Lovaza Statistical Review) at 5-6; PDX 6-8; Trial Tr. 1587:4–1590:11 (Toth Direct). These differential effects are summarized in PDX 6-8:



715. A person of ordinary skill would have expected LDL-C to go up dramatically if EPA were administered to patients with severe hypertriglyceridemia—just as with all approved TG-lowering agents at the time. Trial Tr. 1665:17–1669:16 (Toth Direct). A person of ordinary skill at the time of the invention would have understood that LDL-C increases in the severely hypertriglyceridemic were a "general phenomenon" that occurred irrespective of which TG-lowering agent was used—a necessary consequence of the mechanism of lowering TGs by converting VLDL to LDL. *See supra* ¶¶ 33–34, 39–53. A person of ordinary skill– therefore would have expected that high purity EPA would produce large increases in LDL-C in patients with

severe hypertriglyceridemia—just as all prior art approved treatments for severe hypertriglyceridemia had done. *See supra* ¶¶ 33–34, 39–53.

716. Other evidence from around the time of invention confirms this view. For example, in December 2008, Amarin convened an expert panel to elicit their views about the development project that led to VASCEPA®. One panelist told Amarin that with high purity EPA "LDL-C is likely to go up as it does with virtually all [TG] lowering therapies in this group of patients [having severe hypertriglyceridemia]" and another told Amarin that it should be "very careful" about working with patients whose baseline TGs were between 500 and 650 mg/dL because they would have "relatively high IDL and therefore treatment is likely to increase the conversion of IDL to LDL in these patients—thus pushing up LDL-C." PX 754 (Expert Panel Notes) at 2; *see also* Osterloh Dep. 183:15–187:4 (discussing skepticism of experts at Amarin's 2008 Expert Panel Meeting).

717. Even after 2008, moreover, the understanding continued to be that TG-lowering agents worked to lower TGs in the severely hypertriglyceridemic population by increasing lipoprotein lipase activity, thereby increasing the conversion of VLDL to LDL and, in the process, raising LDL-C. For example, the VASCEPA Medical Review from 2011 reflected FDA's understanding that Lovaza's mechanism for lowering TGs was enhanced conversion of VLDL to LDL—and that this explained the large increase in LDL-observed with Lovaza in patients with very high TGs. *See* PX 289 (VASCEPA Medical Review) at 14 ("The increase in LDL-C [with Lovaza] is thought to be due to the increased activity of LPL [Lipoprotein Lipase] activity. This increased activity enhances the conversion of [VLDL] and [IDL] to LDL-C."); Trial Tr. 860:15–863:18 (Heinecke Cross).

718. Defendants failed to point to anything in the prior art suggesting that substantial increases in LDL-C would be avoided if high purity EPA is given to patients with very severe hypertriglyceridemia. Defendants failed to cite, for instance, even a single prior art reference that taught that high purity EPA would perform differently with respect to LDL-C in patients with very high TGs than Lovaza or fibrates. Nor did Defendants cite prior art teaching that one could avoid

the large LDL increases observed with Lovaza in patients with severe hypertriglyceridemia by changing the composition to include only EPA instead of Lovaza's omega-3 fatty acid mixture. Defendants therefore have fallen *far short* of proving that a person of ordinary skill would have reasonably expected to avoid substantial LDL-C increases by administering high purity EPA to persons with severe hypertriglyceridemia.

719. Similarly, Defendants have fallen far short of proving by clear and convincing evidence that high purity EPA would have been reasonably expected to reduce apo B in patients with severe hypertriglyceridemia. Nowhere did Dr. Heinecke or Defendants cite prior art demonstrating the effect of apo B in persons with very high TGs. Trial Tr. 1779:25–1780:22 (Toth Direct). And the only omega-3 fatty acid formulation in which apo B effects had been measured in patients with severe hypertriglyceridemia did not show a reduction in apo B; it showed a slight increase. PX 939 (Lovaza Statistical Review) at 25, Fig. 7; Trial Tr. 1724:8–1725:11 (Toth Direct).

I. Defendants Have Failed to Adduce Clear and Convincing Evidence That It Was "Obvious to Try" Purified EPA to Reduce TGs in Severely Hypertriglyceridemic Patients without Raising LDL-C

720. An invention may be "obvious to try" only if there are "a finite number of identified, predictable solutions" that lead to "anticipated success." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). "To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identifiable, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Defendants fell far short of meeting this standard.

721. While Defendants contend that there were only three options for pursuing an improved TG-lowering formulation that would not increase LDL-C in patients with severe hypertriglyceridemia, *see* Trial Tr. 760:2–761:5 (Heinecke Direct), a person of ordinary skill in the art in March 2008 seeking to arrive at an improved treatment for severe hypertriglyceridemia that avoided LDL-C increases would have had numerous potential options to pursue, including trying to develop a new niacin or fibrate product, a combination of existing agents, or some new type of TG-lowering agent altogether. Trial Tr. 1707:1–1708:9 (Toth Direct). And even if one had

been limited to fish oil formulations, there was a vast array of choices to pursue, as one could have: (1) varied the ratio between the principal omega-3 fatty acids (in a wide variety of ratios);[19] (2) could have varied the dose; or (3) could have added other substances, such as alpha-linolenic acid (as some people have), omega-6s, or omega-9s. Trial Tr. 1707:1–1708:9 (Toth Direct); PDX 6-29. The list was potentially infinite. *Id.*

722. Among such choices, a person of ordinary skill in the art would not have found it obvious to administer 4 g/day of highly purified EPA with substantially no DHA, given all of the potential advantages the prior art reported for DHA, as well as the fact that EPA raised potential concerns about fasting glucose levels in diabetics, who make up a large portion of persons with very high triglycerides. *See supra* ¶¶ 553–63, 668–703. Nor would a person of ordinary skill in the art have seen an LDL-C advantage with using purified EPA. *See supra* ¶¶ 550–52, 668–703.

723. Moreover, a person of ordinary skill in the art would not have reasonably expected that *any* option would avoid substantial increases in LDL-C in patients with severe hypertriglyceridemia, given that such increases were understood to be a "general phenomenon" resulting from the mechanism by which TG-lowering agents, including omega-3 fatty acids, lowered TGs. *See supra* ¶¶ 39–53. Instead, the person of ordinary skill would have expected that any omega-3 fatty acid formulation, including both pure DHA and EPA, would dramatically increase LDL-C in persons with severe hypertriglyceridemia. *See supra* ¶¶ 39–53, 704–719. Thus, there certainly were not a finite number of "identified, predictable solutions" that lead to "anticipated success." *KSR Int'l Co.*, 550 U.S. at 421.

[19] Around the time of the claimed invention, and even in the years following, researchers continued to pursue omega-3 mixtures in a variety of ratios of EPA and DHA. The clinical trials underway as of 2008 all investigated formulations that included substantial amounts of DHA, including the OMEGA trial (460 mg EPA/380 mg DHA); ALPHA OMEGA (400 mg EPA-DHA); SU.FOL.OM3 (400 mg EPA/200 mg DHA); ORIGIN (465 mg EPA/375 mg DHA); R&P (500 mg EPA/500 mg DHA); DO-IT (1150 mg EPA/800 mg DHA); ASCEND (460 mg EPA/380 mg DHA). *See supra* ¶¶ 142–51. Dr. Fisher himself admitted that, as of 2008, a variety of trials on a variety of mixtures of EPA and DHA were being conducted. Trial Tr. 1183:13–16 (Fisher Cross).

724. Furthermore, real world experience confirms that it would not have been obvious to try a formulation of high purity EPA with substantially no DHA as a treatment for severe hypertriglyceridemia. Although purified EPA had been known since at least the approval of Epadel in the early 1990s, no one as of March 2008 had developed a method of lowering TGs in the severely hypertriglyceridemic population using a composition with highly purified EPA and substantially no DHA. Trial Tr. 889:1–890:1 (Heinecke Cross). Here, the "elapsed time between the prior art and the [asserted patents'] filing date evinces that the [claimed invention] was not obvious to try." *Leo Pharm. Prod.*, 726 F.3d at 13456-57.

725. That the clinical advantages of purified EPA in treating severe hypertriglyceridemia were not obvious from the prior art is further manifest from the fact that GSK and Reliant developed the Lovaza omega-3 mixture in 2004 to treat severe hypertriglyceridemia rather than high purity EPA. Trial Tr. 889:1–19 (Heinecke Cross). Had the benefits of using purified EPA over the mixture in treating severe hypertriglyceridemia been obvious, GSK and its predecessors would not have pursued the mixture instead.

J. Defendants Have Failed to Adduce Clear and Convincing Evidence That It Was Obvious to Treat Severe Hypertriglyceridemia with a Combination of Purified EPA and a Statin to Reduce TGs Without Raising EPA

726. On the last day of trial, Defendants suggested that the Asserted Claims were obvious over a combination of purified EPA and a statin, on the theory that such a combination would have provided a reasonable expectation of success of lowering TGs without increasing LDL-C in patients with severe hypertriglyceridemia. *See* Trial Tr. 1871:16–1877:2 (Toth Cross).

727. But Defendants did not assert such a combination in their Pretrial Findings of Fact, or in affirmative testimony. Prior to trial, Defendants made clear they were proceeding on a single obviousness theory, and a single combination of prior art references—Lovaza PDR (DX 1535), Mori 2000 (DX 1538) Hayashi (DX 1532) and Kurabayashi (DX 1534). *See* Defs.' Proposed Findings of Fact, Conclusions of Law, and Order of J. ¶ 389 (ECF No. 336) ("For all Asserted Claims, as discussed in greater depth below, a skilled artisan would have combined the following prior-art references: Lovaza PDR (DX 1535), Mori 2000 (DX 1538), Hayashi (DX 1532) and

Kurabayashi (DX 1534).").[20] At trial, Dr. Heinecke confirmed that Defendants were proceeding on this single combination. S*ee* Trial Tr. 718:20–719:3 (Heinecke Direct); *see also id.* 828:10–22 (Heinecke Cross). Defendants therefore should not be entitled to raise a new obviousness theory and combination now.

728. In any event, the Asserted Claims are not obvious over such a combination, even if permitted. *First*, Defendants have failed to show motivation to combine purified EPA and a statin to treat severe hypertriglyceridemia. The purported motivation that Defendants have offered for why a person of ordinary skill would have wanted to modify Lovaza is to avoid the need to co-administer a statin. *See* Trial Tr. 813:8–19 (Heinecke Direct) ("Q: Even though LDL-C could be reduced with statins, was there still a motivation to improve Lovaza to avoid increases in LDL-C? A: Yes, there is. Obviously patient compliance is a major issue in clinical medicine. For example, most patients prescribed statins don't take them after six months. . . . It's clearly easier to take one pill, for example, of pure EPA to treat a condition than to combine two pills such as Lovaza with a statin."). Defendants' new obviousness theory is contradicted by this purported motivation.

729. *Second*, Defendants' new theory also fails to establish motivation to co-administer a statin with *high purity EPA*. As noted above, the prior art taught that DHA had advantages over EPA, so a person of ordinary skill would have seen no reason to use a formulation with *high purity EPA* and substantially no DHA, even if they were going to combine an omega-3 fatty acid with a statin. *See supra* ¶¶ 553–63, 673–703.

730. *Third*, the Asserted Claims require that the purified EPA itself not raise LDL-C while reducing TGs in severe hypertriglyceridemia patients. *See generally* Asserted Claims. Whether that rise can be negated through some other agent, such as a statin, is a separate question—and cannot be used in trying to make the case that there would have been a reasonable expectation of avoiding LDL-C increases with EPA when administered to severely hypertriglyceridemic patients.

[20] The only exception was for Claim 16 of the '728 Patent, for which Defendants proposed adding WO '900. ECF No. 336, ¶ 389.

731. In any event, there would have been no reasonable expectation of avoiding LDL-C increases in patients with severe hypertriglyceridemia, even if high purity EPA were co-administered with a statin. A person of ordinary skill would have been aware of no data showing that co-administration of a statin with EPA would negate the large anticipated LDL-C increases in patients with severe hypertriglyceridemia—and Defendants cited none.

732. On cross-examination, Defendants attempted to make do with data from a version of the Lovaza prescribing information showing that co-administration of a statin in patients with TGs of *200 to 499* mg/dL resulted in a 3.5% increase in LDL-C compared to placebo. DX 1578 (Lovaza Prescribing Information) at 1; Trial Tr. 1872:13–1873:2 (Toth Cross); *see also* Trial Tr. 1957:10–23 (Toth Re-Direct). Defendants implied that a person of ordinary skill would have understood that, in view of this data, use of a statin would have completely negated the large LDL-C increases expected in severe hypertriglyceridemia patients with EPA alone. DX 1578 (Lovaza Prescribing Information) at 1, Tbl.1; *see also* Trial Tr. at 1872:13–1873:2 (Toth Cross).

733. But the prior art showed that increases in LDL-C were dramatically greater in patients with severe hypertriglyceridemia compared to patients with TGs below 500 mg/dl. *See supra* ¶¶ 39–53, 704–18. Consequently, a person of ordinary skill in the art would not have understood that statins could negate the much larger anticipated LDL-C increases in patients with *severe hypertriglyceridemia*.

734. Defendants may cite snippets of Dr. Toth's testimony in an attempt to support their theory that statins "could" prevent LDL-C increases in patients with severe hypertriglyceridemia. Trial Tr. at 1874:10–15 (Toth Cross) ("It could. I would qualify it with the word 'could.'"). But Dr. Toth testified that whether one could negate the LDL-C elevation would depend upon the "magnitude of the elevation" and the "baseline TG level." Trial Tr. at 1879:9–15 (Toth Cross). And Defendants point to no data or prior art reference teaching that with the typical magnitude of LDL-C elevation in patients with very high TGs with TG-lowering agents, statins could negate the rise in LDL-C.

K. Defendants' Attempted Eleventh Hour Reliance on the 2007 Lipitor Labeling Is Procedurally Improper and Factually Unavailing

735. On the last day of trial, during cross-examination of Plaintiffs' expert Dr. Toth, Defendants identified for the first time the 2007 approved Lipitor labeling as prior art in support of an assertion that statins were approved in the prior art to treat severe hypertriglyceridemia. *See* DX 3007 (Lipitor Label 2007); Trial Tr. 1809:1–13 (statement of Mr. Klein). Defendants' eleventh-hour assertions regarding the use of statins in the prior art is both procedurally improper and factually unavailing, as the effect of statins would not have provided a person of ordinary skill in the art in 2008 with any reasonable expectation concerning the effects of EPA.

736. First, Defendants' attempt to establish that statins were approved to treat severe hypertriglyceridemia *in the prior art* through the eleventh hour identification of the 2007 Lipitor labeling is improper. Section 282 of the Patent Code, 35 U.S.C. § 282, expressly requires that all prior art used by an accused infringer be identified at least 30 days before trial:

> In actions involving the validity or infringement of a patent the party asserting invalidity or noninfringement shall give notice in the pleadings or otherwise in writing to the adverse party at least thirty days before the trial, of … the title, date, and page numbers of any publication to be relied upon … as showing the state of the art ….”

737. As the Federal Circuit has observed, “[t]he objective of section 282's provision for advance notice is to prevent unfair and prejudicial surprise by the production of unexpected and unprepared-for prior art references at trial.” *Eaton Corp. v. Appliance Valves Corp*., 790 F.2d 874, 879 (Fed. Cir. 1986). Thus, it has cautioned that “notice of prior art must not be such as effectively to preclude an opportunity for the opposing party to prepare to address it at trial. Witnesses may have to review the document(s), and rebuttal evidence may have to be sought out and examined. The documents noticed to the opposing party may shape the course of the trial.” *Id.*

738. Defendants indisputably failed to comply with Section 282. Though Defendants had identified the **current, 2019** Lipitor label (DX 1986), for use in their non-infringement case. *See* Trial Tr. 640:19–641:19 (Sheinberg Direct). They did not, prior to the last day of trial, identify any prior art statin labeling, let alone assert that statins were approved as treatments for severe

hypertriglyceridemia in the prior art until the last day of trial. Indeed, Defendants' counsel acknowledged as much in seeking admission of DX 3007, the prior art Lipitor label, at trial. *See* Trial Tr. 1811:4–6 (MR. KLEIN: "the only reason I want [to] move this label in is to make the record clear that this—that the language was in the prior art"). Before this, Defendants had themselves repeatedly taken the position—consistent with all the record evidence to date—that the category of TG-lowering drugs used to treat severe hypertriglyceridemia included niacin, fibrates, and omega-3-fatty acid products; at no point did Defendants identify Lipitor as a prior art treatment for reducing TGs in severely hypertriglyceridemic patients. *See, e.g.*, Trial Tr. 851:15–18 (Heinecke Cross) ("The drugs approved to treat very high triglycerides are fibrates, niacin, Lovaza, Epanova, Omtric [*sic:*Omtryg], and Vascepa"); Trial Tr. 1231:22–1232:19 (Hoffman Direct) (identifying the category of "prescription, triglyceride-lowering drugs as including niacin, fibrate, and omega-3 products"); DDX 8.8 (same).[21] Defendants' sudden switch on the last day of trial to assert Lipitor as a prior art treatment for severe hypertriglyceridemia denied Amarin the opportunity to adduce evidence or testimony concerning the issue so as to permit a full and fair examination of the issue. Defendants' conduct here is precisely what Section 282 of the Patent Code is intended to prevent.

739. In any event, Defendants' belated reliance on the prior art Lipitor label, DX 3007, is unavailing, as Defendants' assertions about the use of statins in the prior art is both factually incorrect and irrelevant.

740. First, Defendants are wrong that statins were approved to treat severe hypertriglyceridemia. As Dr. Toth explained during cross-examination, Lipitor is approved for treatment of hypertriglyceridemia, not severe hypertriglyceridemia. Trial Tr. 1808:17–20 (Toth Cross) ("It had no indication to treat severe hypertriglyceridemia at all."); *id.* at 1971:8–10 (Toth Re-Direct) ("Q. And are statins approved to treat very high triglycerides. A. No."). Defendants' own expert agreed that statins are not approved to treat severe hypertriglyceridemia. Trial Tr.

[21] Nor did Defendants identify any statin labeling in their Pretrial Proposed Findings of Fact or Conclusions of Law. *See* D.I. 333 at ¶¶ 202–306 (Defendants' review of prior art references).

842:13–16 (Heinecke Cross) ("Q: It is correct, is it not, Dr. Heinecke, that statins are not approved to treat very high triglycerides? A: It's correct that it's not approved . . ."). And the 2007 Lipitor Label upon which Defendants base their entire argument makes clear that the drug is indicated for treatment "Hypertriglyceridemia (Fredrickson Type IV)" and had not been studied in Fredrickson Type V as would be required to obtain approval for treatment of *severe* hypertriglyceridemia. *See* DX 3007 (Lipitor Label 2007) at 11, 15; Trial Tr. 1976:6–14 (Toth Re-Direct); *see also* PX 989 (ATP-III) at 90 ("High triglycerides equate to the older definition of type 4 hyperproteinemia, whereas very high triglycerides were called type 5 hyperproteinemia.").

741. Defendants, during cross-examination of Dr. Toth, emphasized that the clinical study in the Lipitor label included patients above 500 mg/dL. However, as Dr. Toth explained, because the study included patients both below and above 500 mg/dL and did not separately report the effects on either group, it is impossible from the labeling to draw any conclusions about the effects of the drug on patients above 500 mg/dL. Trial Tr. 1817:11–1818:7 (Toth Cross) (discussing DX 3007 (Lipitor Label 2007) at 12, Tbl. 4). Also significant is the fact that the Lipitor label reports that some patients experienced a 40 or 50% **increase** in triglycerides from the drug, "not an effect you would want to see" in severely hypertriglyceridemic patients. DX 3007 (Lipitor Label 2007) at 12, Tbl. 4; Trial Tr. 1977:11–15 (Toth Re-Direct). The 2007 Lipitor label thus does not, contrary to Defendants' assertion, provide clear and convincing evidence that statins were understood in the prior art to be useful TG-lowering agents for the treatment of severe hypertriglyceridemia.

742. Indeed, the actual prior art of record discussing the use of statins affirmatively refutes Defendants' position. ATP-III, for example, states that statins were not appropriate for use as a "first line agent for very high triglycerides" because "statins [are] not powerful triglyceride lowering drugs." *See* PX 989 (ATP-III) at 194; DX 1876 (ATP-III) at 181; Trial Tr. 1970:16–1971:3 (Toth Re-Direct). Similarly, the Bays 2008 review explains that statins only "modestly reduce triglyceride levels" and "are mainly used to lower LDL-C levels. Other lipid-altering agents that are used more specifically to reduce TG levels include niacin, fibrates, and omega-3 fatty

acids." *See* PX 486 (Bays 2008) at 2. By contrast, Defendants identify no prior art actually recommending or identifying statins as TG-lowering agents useful for the treatment of severe hypertriglyceridemia. This absence is telling, particularly in light of Defendants' burden to prove obviousness with clear and convincing evidence.

743. Second, even were Defendants correct that statins were described in the prior art as treatment for severe hypertriglyceridemia (and they are not), that would nonetheless be irrelevant. As the Bays 2008 article expressly notes, "Statins & P-OM3 [prescription omega-3 fatty acids] reduce TG levels by different mechanism." PX 486 (Bays 2008) at 9. Statins inhibit the HMG-CoA enzyme, reducing cholesterol synthesis and increasing clearance of LDL through up-regulation of the LDL receptor. As Bays 2008 reports, the effect on TG levels is indirect: "Up-regulated LDL receptors may also increase clearance of other TG-containing lipoproteins, at least partially accounting for the modest TG lowering effects of statins." *See* PX 486 (Bays 2008) at 9; Trial Tr. 1975:3–15 (Toth Re-Direct). There is no evidence that omega-3 fatty acids inhibit the HMG-CoA enzyme, and neither DHA or EPA is believed to act like a statin. Trial Tr. 1975:16–21. Instead, omega-3 fatty acids are repeatedly described in the prior art to reduce TGs in severely hypertriglyceridemic patients in the same way as fibrates and niacin: through enhanced conversion of the TG-rich VLDL particles to LDL particles. *See, e.g.,* PX 486 (Bays 2008) at 9-12; PX 923 (McKenney I) at 5; *see also* PX 289 (VASCEPA FDA Medical Review) at 14. Defendants thus provide no basis—let alone a clear and convincing one—to suggest that a POSA in 2008 would look to statins, rather than fibrates, niacin, or Lovaza, in trying to predict the effects of purified EPA in severe hypertriglyceridemia.

L. Amarin's Internal Documents and Investor Presentations Are Not Relevant to the Issue of Obviousness

744. In an effort to prove obviousness, Defendants also repeatedly pointed to statements made by Amarin regarding the prior art and the effects that the inventors and Amarin expected purified EPA to have on LDL-C in severely hypertriglyceridemic patients. *See, e.g.*, Trial Tr. 1830:12–1831:23 (Toth Cross). Defendants contend that such inventor statements are evidence

that a person of ordinary skill in the art would have had a reasonable expectation of success in avoiding LDL-C increases in patients with severe hypertriglyceridemia. *Id.*

745. Defendants' reliance on these statements is misplaced. According to the Federal Circuit, whose case law is controlling here, the thoughts of an inventor are not relevant. Rather, the relevant inquiry is what a person of *ordinary skill* would have believed: "The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012). "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art *that existed at the time*. The invention must be evaluated *not through the eyes of the inventor*, who may have been of exceptional skill, but as by one of 'ordinary skill.'" *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985); *see also Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("The statutory emphasis [of the obviousness inquiry] is on a person of *ordinary* skill. Inventors, as a class, . . . possess something—call it what you will—which sets them apart from the workers of *ordinary* skill, and one should not go about determining obviousness under § 103 by inquiring into what *patentees* (*i.e.*, inventors) would have known or would likely have done, faced with the revelations of references.").

746. Relying on the inventors' statements would therefore constitute clear and reversible error. So too would relying more generally on Amarin internal statements about the likely effects of EPA. As of March 2008, when the invention was conceived, Amarin was a tiny company of approximately a dozen employees and other Amarin employees had already been exposed to the views and insights of the inventors Trial Tr. 278:11–17 (Ketchum Direct). Indeed, when providing information to his colleagues at Amarin, Dr. Manku was not only communicating with his fellow scientists—like Dr. Ian Osterloh—but was also communicating with business-focused individuals like Stuart Sedlack. *See, e.g.*, PX 472 (Mar. 24, 2008 M. Manku E-mail) at 1 (describing his views on how EPA affects certain biomarkers to Dr. Ian Osterloh, Stuart Sedlack and others); Manku Dep. 147:11–17 (describing the March 24, 2008 e-mail as him "trying to bring to [my colleagues']

attention what my thoughts are about – and they are asking me questions and I am replying to their questions with my thoughts."); *see also* Manku Dep. 186:3–8 (explaining that Stuart Sedlack "was in charge of business development.").

747. This is evidenced by the fact that statements by Amarin employees predicting how purified EPA would affect TGs and LDL-C levels in severely hypertriglyceridemic patients tracked the statements Dr. Manku made when attempting to convince his colleagues that purified EPA would not increase LDL-C in these patients. *See* PX 475 (Mar. 16, 2008 M. Manku E-mail) at 1. Moreover, Mr. Sedlack, the custodian of a March 2008 internal Amarin document that Defendants cite, relied on Dr. Manku's technical knowledge EPA's biochemical effects. *See* PX 472, (Mar. 24, 2008 M. Manku E-mail) at 1 (explaining to the Amarin team Dr. Manku's belief that EPA would not increase LDL and would have other beneficial effects on cardiovascular biomarkers). Consequently, it is improper to read the prior art references in this case in view of Amarin internal documents, which interpret the prior art references "through the lens of what [Amarin and the inventors] had invented." *See, e.g.*, *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019).

748. The internal documents and Amarin statements are precisely the type of evidence about which the Federal Circuit was concerned in cases like *Otsuka*, *Standard Oil*, and *Interconnect*. The statements on which Defendants rely reflect the views of the patentee—Amarin—and therefore have no connection to how a person of ordinary skill would have viewed the use of EPA for treating severe hypertriglyceridemia at the time of the invention. When making these statements, Amarin (and the inventors of the Asserted Patents) had years of specialized experience working with EPA that a person of ordinary skill would not have had. *See supra* ¶¶ 59–79. Similarly, when analyzing publications available at the time, Amarin viewed those publications through the prism of its (and the inventors') vast experience with EPA; the person of ordinary skill would not read the publications in the same light. *See, e.g.*, *Neptune Generics*, 921 F.3d at 1377 ("As the Board found, the views Lilly expressed about the prior art references in its communications [with FDA] are made *through the lens of what they had invented*. Therefore, it

declined to read the other prior art references in view of these communications. In doing so, the Board did not err.").

749. For example, Defendants pointed to an internal Amarin document entitled "Cardioprotective Effects of Omega-3 Fatty Acids." DX 1829 (Amarin Internal Report); *see also* Trial Tr. 1830:7–1831:23 (Toth Cross) (discussing internal Amarin report, DX 1829). Although the document lists no date or author, other than Amarin generally, Defendants pointed to the metadata corresponding to this document, which lists a "Create Date" of 3/20/2008 and a "Custodian" of Stuart Sedlack. DX 2241 (AMRN00731643 Metadata) at 1. But as noted above, Dr. Manku—the first-named inventor on the Asserted Patents—was at Amarin at that time and was in communication with Mr. Sedlack. *See supra* ¶¶ 746–47; *see also* PX 472 (Mar. 24, 2008 M. Manku E-mail) at 1 (describing his views on how EPA affects certain biomarkers to Dr. Ian Osterloh, Stuart Sedlack and others); Manku Dep. 147:11–17 (describing the March 24, 2008 e-mail as him "trying to bring to [my colleagues'] attention what my thoughts are about – and they are asking me questions and I am replying to their questions with my thoughts."); Manku Dep. 186:3–8 (explaining that Stuart Sedlack "was in charge of business development.").

750. This internal Amarin document is not relevant to the analysis. As an internal Amarin document, it not available to a person of ordinary skill at the time of invention, and Defendants certainly have not established the contrary.

751. In addition, because the document does not list an individual author, it is best characterized as authored by Amarin. *See* Trial Tr. 276:4–6 (Ketchum Re-Direct). And, as Dr. Ketchum testified, this document was created at a time when Amarin consisted of "maybe marginally beyond a dozen employees," Trial Tr. 276:11–15 (Ketchum Re-Direct), which included the inventors of the patents, Trial Tr. 278:11–17 (Ketchum Re-Direct). Consequently, there is no basis to assume that the inventors did not contribute to the interpretation of the prior art expressed in this document. Indeed, the statements predicting how purified EPA would affect TG and LDL-C levels in severely hypertriglyceridemic patients parallels the statements Dr. Manku made when

attempting to convince his colleagues that purified EPA would not increase LDL-C in these patients. *See* PX 475 (Mar. 16, 2008 M. Manku E-mail) at 1.

752. The remaining Amarin documents on which Defendants rely suffer from the same defect. *See, e.g.*, Trial Tr. 1831:25–1833:1 (Toth Cross) (discussing August 3, 2009 Amarin presentation); *id*. at 1833:4–1834:18 (Toth Cross) (discussing March 2010 Amarin presentation). By virtue of these documents' origination with Amarin, the patentee, the interpretation of the prior art references therein is necessarily made through the lens of what Amarin's employees invented.

753. In addition, not only are these Amarin documents unrelated to the knowledge of persons of skill in the art, but many of them also have no bearing on how such a person would read the prior art *at the time of invention* because they post-date the invention. *See, e.g.*, Trial Tr. 1831:25–1832:7 (Toth Cross) (discussing August 3, 2019 Amarin presentation); *id*. at 1833:4–17 (Toth Cross) (discussing March 2010 Amarin presentation). *See also Neptune Generics*, 921 F.3d at 1377 (affirming the PTAB's decision not to read prior art in view of statements from the patent owner where such statements "were made in December 1999, *more than five months after the critical date*" (emphasis added)).

754. In any event, the very internal documents upon which Defendants rely expressly state that the prior art does not concern severely hypertriglyceridemic patients. *See, e.g.*, PX 474/DX 1854 (Mar. 13, 2008 M. Manku E-mail) at 1 ("It is clear that M[o]chida have not looked at patient population which has Tgs greater than 500mg/dl."). That the *inventors* had particular insight in analyzing the prior art is not relevant to whether the person of *ordinary* skill would not have viewed the prior art and reasonably expected success in avoiding increases in LDL-C in patients with severe hypertriglyceridemia. For the reasons discussed above, that person of ordinary skill would not.

M. The Specification of the Asserted Patents Is Not Relevant to Whether There Was a Reasonable Expectation of Success

755. On the last day of trial, Defendants contended that a trio of cases identified by Defendants' counsel in response to an evidentiary objection—*Merck & Co. v. Teva Pharm. USA*,

Inc., 395 F.3d 1364 (Fed. Cir. 2005), *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362 (Fed. Cir. 2012), and *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326 (Fed. Cir. 2014)—are dispositive of the issue of the obviousness of the Asserted Claims. Trial Tr. 1795:1–15. Apparently, Defendants will argue that if the Asserted Patents do not contain clinical data showing the effects of EPA on LDL-C in the severely hypertriglyceridemic population, then the prior art need not contain any such clinical data to establish a reasonable expectation of success. Defendants' reliance on these cases is misplaced.

756. The cases relied upon by Defendants note that the patents-in-suit themselves lacked clinical data, but they did not hold that the standard for reasonable expectation of success is eliminated or relaxed in such cases—or eliminate the requirement that reasonable expectation of success be shown based *on the prior art*. *See, e.g.*, *Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 287 F. Supp. 3d 505, 517 (D. Del. 2017), *aff'd*, 923 F.3d 1051 (Fed. Cir. 2019) ("The *Merck* court did not hold that a patentee may never rely on the absence of clinical data in the prior art when the asserted patent does not contain clinical data."). Indeed, the question for obviousness is "whether the claimed invention would have been obvious in view of the *prior art*." *Allergan, Inc. v. Sandoz*, 796 F.3d 1293, 1310 (Fed Cir. 2015) (emphasis in original). To the extent Defendants suggest that there would have been a reasonable expectation of success in achieving the claimed invention *because of the specification* of the Asserted Patents, they improperly conflate the issues of obviousness and written description.

757. In the cases relied upon by Defendants, the prior art either did not suggest that the patented method would fail or suggested that the patented method would actually succeed. *See generally Merck*, 395 F.3d 1364; *Alcon*, 687 F.3d 1362; *Hoffmann-La Roche*, 748 F.3d 1326. In that context, the decisions pointed to the absence of any real distinction between what the prior art taught and what the patents-in-suit disclosed as indicative of the absence of any real invention. The facts of this case are radically different, and in a number of ways.

758. First, the prior art *in this case* suggested that the claimed methods—of administering EPA to reduce TGs in severely hypertriglyceridemic patients without substantially

increasing LDL-C—would fail because TG-reducing agents were understood to inherently and dramatically increase LDL-C in severely hypertriglyceridemic patients. *See supra* ¶¶ 704–18. This alone distinguishes the trio of cases that Defendants belatedly rely upon.

759. Second, the shared specification of the Asserted Patents provides extensive information about the different properties that one would obtain by using the claimed methods, setting forth detailed descriptions of the responses in various biomarkers obtained through delivery of substantially pure EPA to patients with severe hypertriglyceridemia. *See, e.g.*, PX 21 ('728 Patent) at 15, column 4. Among such effects, column 4 makes clear that the inventors understood that administration of EPA results in "no increase in LDL-C levels compared to baseline." *Id.* at 15, column 4, line 10. The shared specification of the Asserted Patents further describes in detail the MARINE Clinical Study design, including the various plasma lipid levels and biomarkers designated as secondary efficacy variables. *Id.* at 20–21.

760. Third, the prosecution history of the Asserted Patents shows the LDL-C effects of the claimed invention were confirmed by the MARINE trial results, which were submitted to the Patent Office prior to allowance of the claims. PX 38 ('727 File History) at 130 (Bays I Declaration ¶¶ 12–13); PX 38 ('727 Patent File History) at 140–48 (attaching the results of the MARINE Clinical Study).

761. The trio of cases relied upon by Defendants are in no way similar, and provide no reason to depart from the well-established practice—required by the Supreme Court and the Federal Circuit—of requiring a finding of a reasonable expectation of success in achieving the claimed invention[22] as a prerequisite to a finding of obviousness. *See, e.g., Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

[22] In the cases relied upon by Defendants, the expectations at issue concerned whether the patented methods would bring about certain *unclaimed* effects. *See generally Merck*, 395 F.3d 1364; *Alcon*, 687 F.3d 1362; *Hoffmann-La Roche*, 748 F.3d 1326. By contrast, in this case, eight of the ten Asserted Claims recite limitations on not increasing LDL-C.

N. The Objective Indicia of Non-Obviousness

762. A wide array of objective indicia reinforce the non-obviousness of the Asserted Claims. "Objective indicia of non-obviousness play a critical role in the obviousness analysis,'" *Leo Pharm. Prods.*, 726 F.3d at 1358, "guard as a check against hindsight bias," *Cyclobenzaprine Hydrochloride Extended-Release Capsule Litigation*, 676 F.3d 1063, 1079 (Fed. Cir. 2012), "must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*,713 F.2d 1530, 1538 (Fed. Cir. 1983).

1. Unexpected Benefits

763. In granting the Asserted Patents, the Patent Office found that the unexpected benefits of using purified EPA to treat severe hypertriglyceridemia, along with the fact that the invention met a long-felt need, outweighed any *prima facie* case of obviousness. PX 380 (Notice of Allowance) at 10–12. But the evidence of unexpected benefits is even stronger now than it was at the time the Asserted Patents issued.

764. The claimed method of reducing TGs in severely hypertriglyceridemic patients using 4g/day purified EPA has the unexpected benefit of improving patients serum lipids: LDL-C does not increase while apo B goes down. *See* Trial Tr. 1718:13–1728:11 (Toth Direct). At the time of the invention, a person of ordinary skill in the art would have expected that a drug containing high purity EPA would dramatically increase LDL-C in the severe hypertriglyceridemia population, just as was seen with Lovaza—which, as the only omega-3 fatty acid formulation approved for treatment of severe hypertriglyceridemia at the time of the invention, was the closest prior art. Trial Tr. 1720:21–1721:16 (Toth Direct); DX 1535 (Lovaza Label 2007) at 3, Tbl. 2 (showing placebo-adjusted LDL-C increase of 49.3% and increase in LDL-C from baseline of 44.5%); PDX 6-8.

765. But surprisingly, VASCEPA showed no such increase in LDL-C, reporting a non-significant placebo-adjusted decrease in LDL-C of 2.3%. *See* PX 807 (MARINE CSR) at 11, 81; Trial Tr. 1590:12–22, 1604:21–1605:21, 1718:21–1722:14 (Toth Direct); *see also* PX 833 (Friedewald Roundtable) at 6 ("**Dr. Friedewald:** Why were the . . . LDL-C results [with

VASCEPA®] a surprise? **Dr. Bays:** They were a surprise because prior studies . . . in patients with very high TGs at baseline, EPA and DHA increase LDL-C by as much as 45%"); Bays Dep. 155:23–56:2 ("[M]y expectation was, prior to getting the results of the MARINE trial, is that the LDL cholesterol levels would rise after administration of AMR101 in patients with very high triglyceride levels.").

766. VASCEPA® also unexpectedly lowered apo B—another predictor of cardiovascular risk—by 8.5% compared to placebo in severely hypertriglyceridemic patients. *See* PX 807 (MARINE CSR) at 79; Trial Tr. 1723:14–1727:21 (Toth Direct). This result was unexpected because Lovaza, the closest prior art, showed a slight increase in apo B levels when administered to patients with severe hypertriglyceridemia. PX 939 (Lovaza Statistical Review) at 25, Fig. 7; Trial Tr. 1724:8–1725:11 (Toth Direct); *see also* PX 833 (Friedewald Roundtable) at 6 ("**Dr. Bays:** Two surprising results of MARINE were a reduction in serum apo B and failure of LDL-C to rise. **Dr. Friedewald:** Why were the apo B and LDL-C results a surprise? **Dr. Bays:** They were a surprise because prior studies of EPA plus DHA showed little change in apo B, and in patients with very high TGs at baseline, EPA and DHA increased LDL-C by as much as 45%."). As with VASCEPA®'s avoidance of an increase in LDL-C, this unexpected result was a difference in kind over Lovaza—the difference between reducing apo B in persons with severe hypertriglyceridemia and not doing so. Trial Tr. 1722:7–14, 1727:6–16 (Toth Direct).

767. Dr. Heinecke contended that a person of ordinary skill would have found VASCEPA®'s reduction in apo B expected over Kurabayashi (DX 1534), Grimsgaard (DX 1530) and Nozaki (DX 1541), which administered EPA to patients with mean TG levels far below 500 mg/dL. Trial Tr. 805:14–806:13 (Heinecke Direct). But a person of ordinary skill in the art would not have looked to those studies when forming an expectation about the effect of EPA in persons with severe hypertriglyceridemia; instead, such a person would have looked the experience with Lovaza®, the only omega-3-fish oil formulation approved for severe hypertriglyceridemia. Trial Tr. 1724:5–1728:11 (Toth Direct).

768. Beyond these unexpected benefits, REDUCE-IT has now shown that administering 4g/day purified EPA to severely hypertriglyceridemic patients has the additional unexpected benefit of substantially reducing cardiovascular risk—including reductions in stroke, myocardial infarction, and cardiovascular death—on top of a statin. *See* PX 1185 (FDA Press Release) at 1 ("Vascepa is the first FDA approved drug to reduce cardiovascular risk among patients with elevated triglyceride levels as an add-on to maximally tolerated statin therapy."); Trial Tr. 849:21–24 (Heinecke Cross) ("Q. So FDA has determined, based on REDUCE-IT, that the effect of EPA on cardiovascular risk in patients with severe hypertriglyceridemia has been determined? A. I'll accept that as being correct."); Trial Tr. 1625:14–21 (Toth Direct) ("Q. Had any [prior] approved triglyceride-lowering agent shown such cardiovascular benefits in patients with very high triglycerides? A. No, counsel."); Trial Tr. 1122:10–14 (Fisher Cross) ("Q. You're not aware of any drug approved for the treatment of severe hypertriglyceridemia that has been shown to have a cardiovascular benefit in severe hypertriglyceridemic patients putting VASCEPA aside[?] A. That is correct."). With the recent failure of the STRENGTH trial, moreover, VASCEPA remains unique in this regard. PX 1219 (STRENGTH Press Release) at 1.

769. VASCEPA is thus the first treatment for reducing TGs in severely hypertriglyceridemic patients that *both* addresses a patient's risk of pancreatitis and reduces their cardiovascular risk. This is a dramatic improvement from the prior art treatments that, by raising LDL-C, were viewed as pro-atherogenic. *See* PX 1026 (Carlson) at 7 ("The finding of *major clinical concern* in this report is the sometimes quite substantial rise in LDL cholesterol."); Trial Tr. 1576:10–1577:25 (Toth Direct).

770. Defendants argue that the REDUCE-IT results were not unexpected in view of JELIS. But JELIS studied a population that had TG levels that were only slightly above normal, with a mean TG of 153 mg/dL. Trial Tr. 1745:6–21 (Toth Direct). A person of ordinary skill in the art as of March 2008 would not have expected that any potential cardiovascular benefits reported in JELIS would be applicable to patients with TG levels of at least 500 mg/dL. Trial Tr. 1769:4–1770:9 (Toth Direct). As of March 2008, a person of ordinary skill would have expected

that an omega-3 fatty acid preparation, including purified EPA, far from reducing LDL-C, would dramatically increase it, thereby increasing cardiovascular risk. Trial Tr. 1574:1-1575:1, 1577:13-1598:17, 1769:1–1770:9 (Toth Direct).[23] Therefore, even if a person of ordinary skill took at face value the reported 19% risk reduction reported in JELIS—which that person would not have done given the study's significant design flaws, *see supra* ¶¶ 624–38—that person would not have understood JELIS as showing any benefit in patients with severe hypertriglyceridemia.

771. Moreover, there can be no dispute that the effect of VASCEPA® on stroke was unexpected in view of JELIS. Trial Tr. 1769:25–1772:13 (Toth Direct). REDUCE-IT showed a statistically significant reduction in stroke of 28%, whereas JELIS reported no benefit in terms of stroke. PX 272 (Bhatt) at 10, Fig. 4; DX 1553 (Yokoyama 2007) at 5, Fig. 3; Trial Tr. 1770:10–1771:13 (Toth Direct). Nor could this difference be termed a mere difference in degree rather than in kind: A reduction in stroke risk (of 28% as compared to 0%) is of tremendous clinical benefit, as strokes are one of the most dreaded cardiovascular events, often leaving patients disabled or unable to speak. Trial Tr. 1771:14–1772:4 (Toth Direct). And for patients who do not experience a stroke because they are taking VASCEPA®, the difference cannot be termed one simply of degree, rather than kind. Trial Tr. 1771:14–1772:4 (Toth Direct).

772. In addition, the effect of REDUCE-IT in reducing cardiovascular death is unexpected over JELIS. Trial Tr. 1772:5–1773:22 (Toth Direct). In REDUCE-IT, VASCEPA® reported a 20% reduction in cardiovascular death, whereas JELIS did not report a significant reduction in cardiovascular death. PX 272 (Bhatt) at 10 Fig. 4; DX 1553 (Yokoyama 2007) at 5, Fig. 3; Trial Tr. 1772:5–1773:1 (Toth Direct). This is a difference in kind over the results reported in JELIS, and a landmark achievement. Trial Tr. 1772:5–1773:22 (Toth Direct).

[23] Those concerns would have been amplified by the use of a 4 g/day dose—which was more than twice the EPA dose in JELIS. In March 2008, a person of ordinary skill would have been concerned that higher doses might result in adverse lipid effects that could exceed an optimal threshold or even interfere with any potential cardiovascular benefits. *See* PX 567 (Nilsen) at 5 ("It is also possible that the high doses [4 g/day] of concentrated n-3 fatty acids applied in this study exceeded some optimal threshold level, outweighing the beneficial effect or even leading to an apparent adverse effect."); Trial Tr. 1708:10–1710:23 (Toth Direct).

773. Moreover, the notion that the results of REDUCE-IT were expected over JELIS is belied by the widespread expression of surprise at the results from REDUCE-IT. *See, e.g.*, PX 959 (Kastelein) at 1 ("We welcome these results with surprise, speculation, and hope. Most surprising was the difference between the results of REDUCE-IT and those of many previous trials of n–3 fatty acids."); PX 952 (O'Connor) at 1 ("'I'm very surprised by the magnitude of the results, which quite frankly are large,' said Dr. Michael J. Blaha, the director of clinical research at the Ciccarone Center for the Prevention of Heart Disease at Johns Hopkins Medical School, who was not involved in the study. 'My expectations were very low. A lot of people are legitimately surprised by this.'"); PX 951 (Feuerstein) at 3 (statement of Dr. Norman Lepor) ("I went into this study not convinced that Vascepa would make a difference, but these results will definitely change my practice and the way I treat patients."); *id.* at 2 (statement of Dr. Ethan Weiss) ("I thought the Vascepa study would be negative, colored by all the prior failed studies so I'm surprised. I'm willing to eat my shoe on this one. This could be really beneficial to people."); *see also* Trial Tr. 1625:25-11633:5 (Toth Direct). Indeed, the results of REDUCE-IT would not have been met with such surprise if JELIS had been understood to establish cardiovascular benefits—in any population—with high purity EPA a decade earlier.

774. It was further unexpected that VASCEPA, a composition of highly purified EPA and substantially no DHA, would contrast so dramatically in its ability to reduce cardiovascular risk in comparison to omega-3 fatty acid preparations containing a mixture of DHA and EPA—the latter of which have consistently failed to demonstrate a significant cardiovascular benefit. *See supra* ¶¶ 142–51. At no point prior to publication of the REDUCE-IT results was it appreciated that an omega-3 product containing at least 96% EPA and substantially no DHA, such as VASCEPA, would so dramatically outperform a DHA/EPA mixture in terms of reduction in cardiovascular risk. Indeed, even in early 2018, just prior to the announcement of REDUCE-IT, publications continued to group purified EPA with DHA/EPA mixtures when concluding that there was no support for use of omega-3 fatty acids in preventing cardiovascular events. *See, e.g.*, PX 954 (Aung) at 1 (concluding on the basis of a meta-analysis that "omega-3 fatty acids had no

significant association with fatal or nonfatal coronary heart disease or any major vascular events" and that there was "no support for current recommendations for the use of such supplements in people with a history of coronary heart disease."); PX 953 (Abdelhamid) at 66 (concluding on the basis of a meta-analysis that "[s]upplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little."). It never occurred to commentators that purified EPA may have special properties that mixtures of EPA and DHA do not have when it comes to reducing cardiovascular risk, thus prompting commentators to continue to group these together.

775. ***Nexus.*** There is a nexus, or relationship, between the Asserted Claims and all of the objective indicia of non-obviousness, including unexpected results and others detailed below. First, there is a rebuttable presumption of nexus when objective indicia are tied to a specific product, whose use according to the product label embodies the invention disclosed and claimed in the patent. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). Because use of VASCEPA according to its product label embodies the Asserted Claims, and the objective indicia are tied to VASCEPA, there is a presumption of nexus. *See supra* § XI. Defendants nowhere rebutted this presumption.

776. Additionally, the unexpected benefits and other objective indicia are linked to the features of the Asserted Claims, including the claimed composition (at least about 96% EPA by weight of all fatty acids present and substantially no DHA); its daily dose of 4g/day over a period of 12 weeks or greater; its avoidance of substantial increase in LDL-C in patients with TG levels of at least 500 mg/dL, even in patients not on concomitant lipid altering therapy; and its lowering of TGs, and reduction in apo B in, individuals having at least 500 mg/dL. Trial Tr. 1604:6–1633:5, 1710:24–1778:8 (Toth Direct).

777. Defendants contend that there is a lack of nexus between the Asserted Claims and the objective indicia relating to the REDUCE-IT trial, but none of these arguments has merit. Carrying out the claimed invention—administering 4g/day of purified EPA to reduce TGs in severely hypertriglyceridemic patients—improves patients' cardiovascular risk profile and moves

the patients towards reduced cardiovascular risk. Trial Tr. 1615:14–1633:5 (Toth Direct). Defendants' arguments to the contrary are mistaken.

778. *First*, Defendants dispute nexus relating to REDUCE-IT because the Asserted Claims are directed to persons with very high triglycerides, whereas REDUCE-IT's inclusion criteria included a TG range from 135 mg/dL to 499 mg/dL. Trial Tr. 818:12–21 (Heinecke Direct). But as noted above, the 499 mg/dL cap on TGs applied only at *enrollment*, not when patients began to take the study medication, and REDUCE-IT in fact did include patients with TG levels exceeding 500 mg/dL. *See supra* § XI. Moreover, REDUCE-IT showed that the cardiovascular benefits observed in REDUCE-IT apply to patients with very high TGs, with a tertile analysis showing that cardiovascular benefits accrue in patients independent of baseline TGs, including in patients with TGs of at least 500 mg/dL. *See supra* ¶¶ 159–69.

779. That VASCEPA provides a cardiovascular benefit in patients with very high TGs has been recognized by FDA. After reviewing the REDUCE-IT results, FDA expanded the approved use of VASCEPA to include an indication for reduction in cardiovascular risk in persons with TG levels over 150 mg/dL, including patients with severe hypertriglyceridemia. *See supra* ¶¶ 165–69. Furthermore, in approving the expanded indication, FDA removed the Limitation of Use that stated "[t]he effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined"—thus recognizing VASCEPA's cardiovascular benefit in patients with severe hypertriglyceridemia. *Compare* PX 940 (VASCEPA Prescribing Information (2017)) at 2 *with* PX 1186 (VASCEPA Label 2019) at 2 (VASCEPA Prescribing Information (2019)) at 2. Thus, FDA determined that VASCEPA was safe and effective for administration to patients with very high TGs. *See supra* ¶¶ 165–69.

780. *Second*, Defendants dispute nexus relating to REDUCE-IT on the ground that the Asserted Claims cover at least a 12-week course of treatment, while the statistically significant reductions in cardiovascular risk reported in REDUCE-IT did not manifest until a year or more of treatment. Trial Tr. 819:19-820:12 (Heinecke Direct). But the fact that statistically significant reductions in cardiovascular risk are not manifest at 12 weeks does not mean that there is no

cardiovascular advantage to a patient who has taken VASCEPA for 12 weeks compared to a patient who has not. Trial Tr. 1775:18–1777:9 (Toth Direct). Indeed, taking VASCEPA for 12 weeks will get patients closer to the point at which they *will* experience significant cardiovascular risk reductions, which by itself is a benefit. Trial Tr. 1776:21–1777:4 (Toth Direct). During that time, moreover, patients experience changes in their biochemistry beyond reductions of triglycerides, including changes in VLDL-C, Lp-PLA2, apo B, and non-HDL as compared to placebo that help lay the foundation for cardiovascular benefit. *See* PX 807 (MARINE CSR) at 105, Fig. 8; Trial Tr. 1775:18–1777:9 (Toth Direct).

781. *Third*, Defendants contend that there is no nexus because the benefits in REDUCE-IT do "not result from a method of reducing triglycerides." Trial Tr. 816:18–817:5 (Heinecke Direct). But whether or not the *mechanism* that produces the cardiovascular benefits observed in REDUCE-IT is TG-lowering is beside the point. There is no requirement that a patent holder must claim the particular mechanism that brings about the objective benefits. *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("reliance on an unexpected property not disclosed in the application may be entitled to weight if 'directed to that which would inherently flow from what was originally disclosed.'") Instead, what matters is whether carrying out the *claimed method*—here, of administering 4g high purity EPA to patients with very high TGs, *i.e.*, VASCEPA®—will produce cardiovascular benefits. *See id.* In this case, it does. Trial Tr. 1615:14–1633:5 (Toth Direct).

782. *Fourth*, Defendants dispute nexus on the ground that the Asserted Claims do not mention cardiovascular risk. Trial Tr. 817:10–12 (Heinecke Direct). But the cardiovascular risk reduction in REDUCE-IT is achieved by carrying out the methods of the Asserted Claims, *see supra* ¶ 777, which is all that is needed for there to be a connection to the claims. There is no requirement that a patent holder specifically claim the unexpected results or other objective indicia. *See Sanofi-Aventis Deutschland GmbH*, F.3d at 1360 ("patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest"); *Knoll Pharm. Co. Inc. v. Teva Pharm. USA Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)

("There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity.")

783. *Fifth*, Defendants dispute nexus for the claims that specify that the method does not substantially increase LDL-C on the ground that the cardiovascular risk reduction in REDUCE-IT does not result from the absence of an LDL-C increase when VASCEPA is administered. Trial Tr. 820:15–821:1 (Heinecke Direct). But the results in REDUCE-IT are the result of carrying out the claimed method of administering 4g high purity EPA to patients with severe hypertriglyceridemia, and consequently, there is necessarily a connection between the REDUCE-IT benefits and the Asserted Claims. In addition, that VASCEPA avoids large rises in LDL-C in patients with very high TGs is an important reason why the cardiovascular benefits of VASCEPA extend to patients with very high TGs, as large increases in LDL-C could otherwise negate such increases. Trial Tr. 1577:13–1578:11 (Toth Direct); Trial Tr. 1769:1–1770:9 (Toth Re-Direct).

784. *Sixth*, Defendants dispute the nexus between the benefits observed in REDUCE-IT and the Asserted Claims forbidding concurrent statin use, such as Claim 1 of the '728 Patent, because all patients in REDUCE-IT were on statins. Heinecke Tr. 821:4–11 (Heinecke Direct). But REDUCE-IT examined the degree to which VASCEPA® offers a cardiovascular benefit *beyond* appropriate statin therapy, and showed that VASCEPA® in fact offers powerful cardiovascular risk reduction *over and above* the risk reduction provided by statins. *See supra* ¶¶ 159–70. Furthermore, statins primarily lower cardiovascular risk by reducing LDL-C, while VASCEPA® reduces cardiovascular risk through a different mechanism. Trial Tr. 1777:16–1778:8 (Toth Direct). That statins and VASCEPA® lower cardiovascular risk through different mechanisms strongly suggests that patients derive cardiovascular benefit even if not on statins. Trial Tr. 1777:16–1778:8 (Toth Direct).

785. Furthermore, the FDA-approved revised prescribing information for VASCEPA® specifies that the indication for cardiovascular risk reduction includes patients on "maximally tolerated statin therapy." *See* PX 1186 (VASCEPA Label 2019) at 1. This includes patients who are not able to tolerate statins or are unwilling to go on them—*i.e.*, patients who are *not on* statin therapy. Trial Tr. 152:4–10 (Ketchum). VASCEPA's expanded indication thus reflects FDA's belief that that patients will benefit from cardiovascular risk reduction—even if not on statin therapy.

2. Satisfaction of Long-Felt Need

786. Further supporting the non-obviousness of the Asserted Claims is that VASCEPA met long-felt needs—as it is the first approved treatment that reduces TGs without raising LDL-C in patients with severe hypertriglyceridemia, and the first treatment for reducing TGs in severely hypertriglyceridemic patients that reduces cardiovascular risk on top of statin. *See* Trial Tr. 1712:1–1716:14, 1728:18–1753:25, 1759:10–1760:2. (Toth Direct).

787. *Satisfaction of long-felt need for a severe hypertriglyceridemia treatment that lowered TGS without raising LDL-C.* Prior to VASCEPA®, there was a long-felt need for a treatment that lowers TGs in patients with severe hypertriglyceridemia without substantially increasing LDL-C. Trial Tr. 1712:1–1716:14 (Toth Direct). All prior approved TG-lowering products for severe hypertriglyceridemia produced large increases in LDL-C in persons with very high TGs, s*ee supra* ¶¶ 39–53, and these increases had long been recognized as a problem. Trial Tr. 1574:3–1575:1, 1712:1–1716:3 (Toth Direct). A 1977 publication by Carlson that examined the effect of niacin in persons with very high TG levels observed, for example, that "the finding of *major clinical concern* in this report [was] the sometimes quite substantial rise in LDL cholesterol." PX 1026 (Carlson) at 7; Trial Tr. 1575:2–1578:11 (Toth Direct).

788. Other prior art published after 1977 continued to express concern about the effect of TG-lowering agents on LDL-C in patients with very high TGs. Trial Tr. 1713:9–1714:13 (Toth Direct). The 1990 prescribing information for the fibrate product Lopid, for example, warned that treatment was associated with a significant increase in LDL-cholesterol in patients with high TG

levels.[24] Trial Tr. 1713:9–16 (Toth Direct). The Lopid label therefore warned that "[p]atients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil." PX 964 (Lopid PDR 1990) at 2; Trial Tr. 1713:18–1714:10 (Toth Direct). Following Lopid, other publications continued to reflect concerns about LDL-C increases with treatments for severe hypertriglyceridemia, such as the 1997 Harris publication, which reported that administration of Omacor (also known as Lovaza) produced a 31% increase in LDL-C when administered to patients with very high TGs. DX 1531 (Harris 1997) at 1; Trial Tr. 1714:23–1715:16 (Toth Direct).

789. The substantial increase in LDL-C associated with approved treatments for severe hypertriglyceridemia was understood to be problematic for two reasons. First, LDL-C was understood to be atherogenic, and an increase in LDL-C was therefore at odds with the secondary goal in treating the severely hypertriglyceridemic—reducing cardiovascular risk. PX 989 (ATP-III) at 194; DX 1876 (ATP-III) at 181, Tbl. VII.2–4; PX 1026 (Carlson) at 7; Trial Tr. 1569:25–1570:19, 1577:13–25 (Toth Direct). Second, the LDL-C increase was understood to interfere with optimal statin use—by blunting or negating their LDL-C lowering effects—even if it was possible to use statins with the TG-lowering agents (and it was not always possible). Trial Tr. 1598:18–1599:18 (Toth Direct).

790. As demonstrated by the MARINE trial, VASCEPA® met a long-felt need by providing for the first time a safe, well-tolerated agent that provides clinically meaningful reductions in TGs in patients with severe hypertriglyceridemia without substantially raising LDL-C. Trial Tr. 1712:1–1718:12 (Toth Direct); PX 807 (MARINE CSR) at 11. VASCEPA® also avoids the severe tolerability issues associated with niacin, as well as the safety concerns associated with fibrates. Trial Tr. 1716:4–14 (Toth Direct).

791. That a minority of patients in the MARINE study experienced increases in LDL-C does not change the fact that VASCEPA met this long-felt need. No drug has a uniform response

[24] While the reference in the Lopid label was to patients with high TG levels, a person of ordinary skill would have understood that LDL-C increases were an even greater concern in persons with very high TGs. Trial Tr. 1713:13–1414:22 (Toth Direct).

in all patients. Trial Tr. 1717:15–1718:1 (Toth Direct); Trial Tr. 1166:10–1167:12 (Fisher Cross). On average, the MARINE trial showed that LDL-C does not increase in patients with severe hypertriglyceridemia, as the median patient in MARINE had a slight decrease in LDL-C. PX 940 (VASCEPA Label 2017) at 6–7, Trial Tr. 1717:15–1718:8 (Toth Direct); Trial Tr. 1166:10–1167:12 (Fisher Cross). Moreover, VASCEPA's FDA approved product labeling makes clear that "the reduction in TG observed with VASCEPA *[i]s not associated* with elevations in LDL-C levels relative to placebo." PX 940 (VASCEPA Label 2017) at 7 (emphasis added).

792. For the same reasons, there is no merit in Defendants' contention that the objective indicia relating to VASCEPA's avoidance in LDL-C is not commensurate in scope with the Asserted Claims, as objective indicia need only be "reasonably commensurate" in scope with the claims.[25] *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

793. There is no merit in Dr. Heinecke's contention that Mori 2000 met the need for a treatment that lowers TGS without increasing LDL-C in patients with severe hypertriglyceridemia. Trial Tr. 808:13–22 (Heinecke Direct). Mori studied *mildly hyperlipidemic* patients—not patients with *severe hypertriglyceridemia*—and therefore could not have satisfied a need experienced by patients with very high TGs. Trial Tr. 1716:15–1717:2 (Toth Direct).

794. Nor is there any merit to the contention that statins met such a long-felt need. Statins were not approved for the treatment of severe hypertriglyceridemia and, as ATP-III observed, statins were "not [a] first-line agent for very high triglycerides (statins not powerful triglyceride lowering drugs)." PX 989 (ATP-III) at 194; DX 1876 (ATP-III) at 181; Trial Tr. 1969:21-1971:10 (Toth Redirect); *see also* PX 486 (Bays 2008) (noting that statins only "modestly" reduce TG levels).

795. In any event, if Defendants were correct that statins previously met the need for a medication that provided clinically meaningful reductions in TGs without raising LDL-C in

[25] For the same reason, the fact that apo B was not reduced in all patients is of no moment, because MARINE showed that, in general, VASCEPA® reduces apo B in patients with severe hypertriglyceridemia. Trial Tr. 1717:15–1718:12 (Toth Direct); PX 807 (MARINE CSR) at 9 (reporting average 9% reduction in apo B).

patients with severe hypertriglyceridemia, it would negate Defendants' entire obviousness case. In such a scenario, there would have been no reason for a person of ordinary skill to contemplate modifying LOVAZA® to try to avoid LDL-C increases, as one could achieve clinically meaningful TG reductions without LDL-C increases in patients with severe hypertriglyceridemia simply by using a statin.

796. Additionally, the combination of statins and Lovaza did not meet the long-felt need for a TG-lowering agent that avoided substantial increases in persons with severe hypertriglyceridemia. As Dr. Heinecke himself observed, a person of ordinary skill would not have found it desirable to use two different pills. Trial Tr. 813:6–19 (Heinecke Direct). Furthermore, many patients are statin-intolerant or can only tolerate sub-optimal statin doses. Trial Tr. 1598:18-1599:18 (Toth Direct). Moreover, even if statins could be used to address the rise in LDL-C from Lovaza, the LDL-C increase blunted the cardiovascular benefit that could otherwise be obtained through LDL-C lowering with statin. Trial Tr. 1715:5–1716:14 (Toth Direct).

797. *Satisfaction of a long-felt need for a severe hypertriglyceridemia treatment that reduced residual cardiovascular risk.* Beyond avoiding LDL-C increases while reducing TGs in persons with severe hypertriglyceridemia, VASCEPA met a long-felt need for a TG-lowering agent that reduces cardiovascular risk on top of statin in severe hypertriglyceridemia patients. Trial Tr. 1728:13–1760:23 (Toth Direct). As noted above, prior to REDUCE-IT, there was a long-felt need for a medication that lowered residual cardiovascular risk beyond the risk reduction provided by statins. *See supra* ¶¶ 130–151. Because elevated TGs have long been recognized as a risk factor for cardiovascular disease, moreover, there was a particular need for a TG-lowering agent that reduced residual cardiovascular risk in persons with elevated TGs, including very high TGs. *See supra* ¶¶ 130–135; *see also* Trial Tr. 1728:18–1753:25, 1759:12–1760:23 (Toth Direct); PX 846 (Austin) at 1.

798. VASCEPA is the first TG-lowering agent to meet this need. It is the first approved TG-lowering agent to demonstrate cardiovascular benefit on top of statins, and the first TG-lowering agent to show cardiovascular benefit in patients with severe hypertriglyceridemia. *See*

supra ¶¶ 159–69; *see also* PX 1185 (FDA Press Release) at 1 ("Vascepa is the first FDA approved drug to reduce cardiovascular risk among patients with elevated triglyceride levels as an add-on to maximally tolerated statin therapy."); Trial Tr. 849:21–24 (Heinecke Cross) ("Q. So FDA has determined, based on REDUCE-IT, that the effect of EPA on cardiovascular risk in patients with severe hypertriglyceridemia has been determined.? A. I'll accept that as being correct."); Trial Tr. 1625:14–21 (Toth Direct) ("Q. Had any [prior] approved triglyceride-lowering agent shown such cardiovascular benefits in patients with very high triglycerides? A. No."); Trial Tr. 1122:10–14 (Fisher Cross) ("Q. You're not aware of any drug approved for the treatment of severe hypertriglyceridemia that has been shown to have a cardiovascular benefit in severe hypertriglyceridemic patients putting VASCEPA aside? A. That is correct."). And prior efforts to demonstrate cardiovascular benefits with a TG-lowering agent on top of statin—with niacin, fibrates, and omega-3s—failed. *See supra* ¶¶ 134–51.

799. Defendants contend that, in light of the JELIS trial, there was no unmet need for a TG-lowering agent that reduced cardiovascular risk. Trial Tr. 824:13-16 (Heinecke Direct). But JELIS did not study or establish any cardiovascular benefit in patients with severe hypertriglyceridemia, as it studied mixed dyslipidemic patients with only slightly elevated TGs, with a mean TG level of 153 mg/dL. DX 1553 (Yokoyama 2007) at 3; Trial Tr. 1744:24–1745:21, 1769:1-1770:9 (Toth Direct); *see also supra* ¶ 622.

800. Moreover, even in the population it did study, JELIS had numerous methodological flaws that prevented the medical community in general from concluding that JELIS established a cardiovascular benefit. *See supra* ¶¶ 624–38. That JELIS (and Epadel) were not understood to have met the long-felt need for a triglyceride-lowering agent that significantly reduced residual cardiovascular risk (in any population) is reflected in the widespread surprise and enthusiasm in late 2018, after publication of the REDUCE-IT results. For example, as noted above, in an editorial in the *New England Journal of Medicine*, the authors welcomed the REDUCE-IT results showing a substantial cardiovascular benefit with VASCEPA® with "surprise, speculation, and hope . . . . After a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a

substantial benefit with respect to major adverse cardiovascular events." PX 959 (Kastelein) at 1–2. And leading doctors observed that REDUCE-IT was a "game changer." *See supra* ¶¶ 170–71, 632. The results of REDUCE-IT would not have been welcomed with such enthusiasm and surprise if the need for a TG-lowering agent that significantly reduced cardiovascular risk had already been solved years earlier by Epadel in JELIS.

801. Moreover, as detailed extensively above, other medical literature reflected the understanding that JELIS did not establish that Epadel provides cardiovascular benefit on top of statin (in any population). *See supra* ¶¶ 632–38. For example, an article in *JAMA Cardiology* published after JELIS, but before REDUCE-IT, concluded that there was "no support for current recommendations for the use of [omega-3 fatty acid] supplements in people with a history of coronary heart disease," including purified EPA—even though the authors were aware of JELIS. PX 954 (Aung) at 1, 3; Trial Tr. 1748:16–1749:14 (Toth Direct). Similarly, the well-respected Cochrane Collaboration concluded before REDUCE-IT that "[s]upplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little"—even though these authors were aware of the JELIS trial. PX 953 (Abdelhamid) at 33, 66; Trial Tr. 1746:9–1748:5 (Toth Direct). If these authors had concluded from JELIS that Epadel significantly lowered residual cardiovascular risk, as Defendants contend, there would have been no such blanket rejection of omega-3 fatty acids.

802. Moreover, as discussed above, Defendants' expert Dr. Fisher was an author of published guidance that did not find JELIS to be evidence of a reduction in cardiovascular risk. *See supra* ¶¶ 634–35; PX 373 (Chapman); Trial Tr. 1127:1–1138:4 (Fisher Cross)

803. Additionally, prior to REDUCE-IT but after JELIS, other guidelines did not recommend high purity EPA to reduce cardiovascular risk. Trial Tr. 1161:17–1162:1 (Fisher Cross). For example, the American Diabetes Association changed its guidelines for addressing cardiovascular risk in 2019 to include EPA following announcement of the REDUCE-IT results.

Id. But as of 2018—after JELIS but before REDUCE-IT—the American Diabetes Association did not recommend EPA. *Id.*

804. Furthermore, FDA's 2013 rejection of Amarin's proposed ANCHOR indication for VASCEPA further undercuts Defendants' contention that Epadel met the long-felt need for a triglyceride-lowering agent that significantly reduced residual cardiovascular risk. As noted above, Amarin had shown in the ANCHOR trial that VASCEPA lowered TGs in patients with baseline TGs of 200–499 mg/dL, and on that basis sought an indication to administer VASCEPA to statin-treated patients in this TG range, on the theory that VASCEPA may provide a cardiovascular benefit to such patients. *See supra* ¶¶ 152–58. But FDA declined to grant the indication without completion of the REDUCE-IT trial, concluding that the available evidence at the time—which included the results from the JELIS trial—was insufficient to conclude that high purity EPA would provide a significant incremental cardiovascular benefit over and above appropriate statin therapy. *See supra* ¶¶ 152–58.

805. Furthermore, the change in VASCEPA labeling before and after REDUCE-IT reveals that FDA did not believe that JELIS established that high purity EPA has a cardiovascular benefit in patients with severe hypertriglyceridemia. After JELIS but prior to REDUCE-IT, the VASCEPA® label specified that "[t]he effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined." PX 940 (VASCEPA Label 2017) at 2. Only following REDUCE-IT was that limitation of use removed. PX 1186 (VASCEPA Label 2019) at 2.

806. Among the reasons that JELIS was not recognized as establishing that Epadel reduces cardiovascular risk were a number of serious design flaws in the study—flaws that FDA recognized. PX 994 (Rosebraugh Decl) at 14-15, ¶¶ 26-27. As noted above, the primary endpoint in the JELIS trial was "any major coronary event"—defined as sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. DX 1553 (Yokoyama 2007) at 2; Trial Tr. 1749:22–1750:3 (Toth Direct). While the trial showed a 19% risk reduction in this primary

endpoint, that result was driven by a single, highly subjective, component: unstable angina. DX 1553 (Yokoyama 2007) at 5, Fig.3; PX 994 (Rosebraugh Decl.) at 14–15, ¶¶ 26–27; Trial Tr. 1750:4–1753:25 (Toth Direct). And given that JELIS was an open label trial, there was serious concern that its reported outcome was the product of bias. *See supra* ¶¶ 627–31.

3. Skepticism

807. Skepticism about an invention is evidence that an invention was not obvious. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Here, skepticism is further evidence that VASCEPA and the Asserted Claims were not obvious, as there was significant initial skepticism about VASCEPA.

808. To begin with, there was skepticism about whether VASCEPA® could avoid a substantial increase in LDL-C in patients with very high TG levels. For example, Amarin hosted a panel of experts in December 2008 to elicit their views regarding AMR101, which was the development project that led to VASCEPA. One panelist told Amarin that "LDL-C is likely to go up as it does with virtually all [TG] lowering therapies in this group of patients [having very high triglycerides]" and another told Amarin that it should be "very careful" about working with patients whose baseline TGs were between 500 and 650 mg/dl because they would have "relatively high IDL and therefore treatment is likely to increase the conversion of IDL to LDL in these patients—thus pushing up LDL-C." PX 754 (Expert Panel Notes) at 2, *see also* Osterloh Dep. 186:4–24, 187:4 (discussing skepticism of experts at Amarin's 2008 Expert Panel Meeting). As these comments reflect, there was initial skepticism that VASCEPA would be able to lower TGs in the severe hypertriglyceridemia population without a substantial increase in LDL-C.

809. There was also skepticism about whether VASCEPA®, along with other omega-3 fatty acid treatments, would be of any benefit in preventing coronary heart disease or otherwise reducing cardiovascular risk. Trial Tr. 1766:2–1768:17 (Toth Direct). Physicians and publications prior to REDUCE-IT expressed general doubt about the cardiovascular benefit of omega-3s, going as far as stating in early 2018, for example, that there was no support for the use of VASCEPA® or other omega-3 fatty acid preparations in patients with cardiovascular risk. *See, e.g.*, PX 954

(Aung) at 1 (concluding on the basis of a meta-analysis that "omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events" and that there was "no support for current recommendations for the use of such supplements in people with a history of coronary heart disease."); PX 953 (Abdelhamid) at 66 (concluding on the basis of a meta-analysis that "[s]upplemental long-chain omega-3 fats are probably not useful for preventing or treating cardiovascular disease, although long-chain omega-3 fats can help to reduce serum triglycerides and raise HDL a little."); Trial Tr. 1766:2–1768:17 (Toth Direct).

810. Moreover, practitioners and medical experts believed that REDUCE-IT would fail to demonstrate a clinical cardiovascular benefit. *See, e.g.*, PX 951 (Feuerstein) at 3 (statement of Dr. Norman Lepor) ("I went into this study not convinced that Vascepa would make a difference, but these results will definitely change my practice and the way I treat patients."); *id.* at 2 (statement of Dr. Ethan Weiss) ("I thought the Vascepa study would be negative, colored by all the prior failed studies so I'm surprised. I'm willing to eat my shoe on this one. This could be really beneficial to people.").

811. REDUCE-IT has put that skepticism to rest, showing that use of VASCEPA® substantially lowers cardiovascular risk over and above the risk reduction provided by statins alone, as reflected in FDA approval for a supplemental indication for cardiovascular risk reduction, including in patients with severe hypertriglyceridemia. *See supra* ¶¶ 159–71.

4. Praise

812. Following initial skepticism, VASCEPA also has been widely praised. Such praise further supports the non-obviousness of the Asserted Claims. *Apple Inc. v. Samsung Elecs.* Co., 839 F.3d 1034, 1053 (Fed. Cir. 2016) (praise is evidence of non-obviousness).

813. VASCEPA®'s ability to lower TGs in severely hypertriglyceridemic patients without increasing LDL-C has been widely recognized. For example, Dr. Richard Castaldo of the Niagara Falls Memorial Medical Center reported that "[s]witching statin add-on therapy from fibrate to icosapent ethyl Vascepa maintained or improved the lipid profile and was well tolerated with no adverse reactions in a series of patients with hypertension and high cardiovascular risk"

and that "important differences between icosapent ethyl and other add-on therapy options include its good safety and tolerability profile and the fact that it does not increase LDL-C levels, as supported by clinical studies and the icosapent ethyl product label." PX 866 (Castaldo) at 2, 6.

814. Dr. Jonathan Fialkow of the Miami Cardiac and Vascular Institute observed that "[u]se of products containing both DHA and EPA . . . require periodic monitoring of LDL-C during therapy due to the potential for increases in this lipid parameter, while treatment with the EPA-only product, icosapent ethyl [VASCEPA] has no LDL-C monitoring requirement." PX 852 (Fialkow) at 5.

815. In reference to the MARINE trial results, Dr. Darren McGuire of University Texas Southwestern observed that "[a]t the end of the day, if you can have favorable cardiovascular effects without raising LDL cholesterol, that's going to be an advantage." DX 1581 (O'Riordan) at 1.

816. The observations of Dr. Steven Nissen, the former chief of cardiology at the Cleveland Clinic after learning of the topline results of the MARINE trial were to similar effect: VASCEPA®'s ability to lower TGs in individuals with very high TG levels without increasing LDL-C has been recognized as a "real advance in the treatment of elevated triglycerides" "because it gives you all the benefit without the downside."[26] DX 1581 (O'Riordan) at 2; Trial Tr. 1610:13–1612:24, 1723:2–13 (Toth Direct).

817. The praise for VASCEPA has only grown since the results of REDUCE-IT were reported. As detailed extensively above, the REDUCE-IT results have been met with "surprise, speculation, and hope" given the "parade of failed cardiovascular outcome trials of fish oils" that

[26] While Dr. Nissen noted some potential caveats about the size, duration, and lack of peer review of the MARINE trial, FDA ultimately had such no concerns about the study design of the MARINE trial (including size and duration) when approving VASCEPA for the treatment of severe hypertriglyceridemia. Trial Tr. 1611:10–1612:6 (Toth Direct). Moreover, the results of the MARINE trial, which only just been announced when Dr. Nissen offered his caveats, were ultimately published in a peer reviewed publication, the *American Journal of Cardiology*. Trial Tr. 1612:7–13 (Toth Direct). And irrespective of his caveats, Dr. Nissen regarded the topline results as exciting, commenting that the MARINE trial showed that "[t]here's still room for small companies to do innovative things in this field." DX 1581 (O'Riordan) at 2.

preceded it, and leading doctors have called the results "phenomenal," a "game-changer," and a "home run" because they showed "for the first time that triglyceride reduction with an appropriate therapy—in this case icosapent ethyl—when used in appropriate doses can make a significant difference." PX 959 (Kastelein) at 1–2; PX 875 (Fidler) at 2 (statement of Dr. Lepor); PX 902 (Hackett) at 1 (statement of Dr. Deedwania); Trial Tr. 1625:22–1633:5 (Toth Direct); *see also supra* ¶¶ 170–71. Some clinicians have considered the REDUCE-IT trial the most significant advance since statin therapy, and national and international groups have embraced the REDUCE-IT results, recognizing VASCEPA® as an add-on to statin therapy and for cardiovascular risk reduction—including the American Diabetes Association, the National Lipid Association, The European Society of Cardiology, and the European Atherosclerosis Society, among others. Trial Tr. 161:6-22 (Ketchum Direct).

5. Commercial Success

818. VASCEPA's commercial success constitutes additional objective evidence of the non-obviousness of the Asserted Claims. *In re Rouffet*, 149 F.3d at 1355. Economic principles suggest that inventions that have commercial value will be developed, and so if companies do not bring a commercially valuable invention to market, that invention must not have been obvious. Trial Tr. 1424:6–15 (Nicholson Direct). Here, substantial and sustained increases in VASCEPA prescription, net sales, and market share, as well as VASCEPA's positive net present value ("NPV"), demonstrate that VASCEPA is a commercial success. Trial Tr. 1423:3–15 (Nicholson Direct).

819. Prescriptions for VASCEPA have grown substantially since the product's launch in January 2013. 174,000 prescriptions for VASCEPA were filled in 2013, and the number increased every year, reaching 1.3 million prescriptions in 2018, an average annual increase of about fifty percent. Trial Tr. 1427:9–17 (Nicholson Direct); PDX 5-6. This increase indicates that patients and health insurers are willing to pay a premium for the features of VASCEPA, given that a relatively inexpensive generic version of Lovaza has been available since 2014. Trial Tr. 1427:18–1428:3 (Nicholson Direct).

820. VASCEPA's net sales have also grown substantially since the product's launch. VASCEPA's net sales were $26 million in 2013 and have increased every year, reaching $228 million in 2018, an average annual increase of 54%. Trial Tr. 1429:2–9 (Nicholson Direct); PDX 5-7. The increase indicates that the product is providing value and that patients and health insurers are willing to pay a premium for the features of VASCEPA. Trial Tr. 1429:10–15 (Nicholson Direct). Defendants' contention that VASCEPA's sales are driven by rebates and discounts is misplaced. The net sales metric relied upon by Dr. Nicholson already accounts for all rebates and discounts. Trial Tr. 1304:17–23 (Hofmann Cross); Trial Tr. 1429:22–1430:5, 1431:3–14 (Nicholson Direct). In any case, the level of rebates and discounts provided for VASCEPA is in line with the industry norm. Trial Tr. 1431:3–14, 1433:12 (Nicholson Direct); PX 746 (QuintilesIMS Institute) at 5, 10.

821. VASCEPA's share of the market for omega-3 fatty acid drugs has also grown every year since its launch. VASCEPA®'s share of omega-3 fatty acid prescriptions was 4% in 2013, increasing to 32% in 2018. Trial Tr. 1435:3–16 (Nicholson Direct); PDX 5-9; PDX 5-10. In contrast, branded Lovaza's share of the same market decreased from approximately 96% in 2013 to under 5% in 2018. Trial Tr. 1436:19–1437:7 (Nicholson Direct); PDX 5-10. VASCEPA®'s share of the broader market for TG-reducing drug prescriptions also increased from 1% in 2013 to 6% in 2018. PDX 5-9. VASCEPA®'s increasing market share is a strong indicator of its increasing value over time. Trial Tr. 1434:8–24, 1435:17–1436:3 (Nicholson Direct). In fact, every TG-reducing drug's prescriptions have been decreasing from 2013 to 2018, whereas VASCEPA®'s prescriptions have been increasing in the same period. DDX 8-7. That VASCEPA® has bucked the trend speaks highly of its performance in the market. Trial Tr. 1438:7–18 (Nicholson Direct).

822. VASCEPA's net present value ("NPV") also demonstrates its commercial success. NPV is the most common method that pharmaceutical companies use to determine whether to launch a new product and to track whether the product is successful. Trial Tr. 1440:1–15, 1444:22–1445:1, 1469:20–1470:7 (Nicholson Direct); PX 600 (Berndt 2015) at 2, 5; PX 602 (Brealey 1996) at 5; PX 612 (Grabowski 2008) at 6. A positive NPV means that the product is more profitable

than the average for similar products in the industry. Trial Tr. 1440:16–1441:14, 1443:18–21 (Nicholson Direct); PX 602 (Brealey 1996) at 16 ("Any time you find and launch a positive NPV project, a project with present value exceeding its required cash outlay, you have made your company's stockholders better off."). VASCEPA®'s NPV is expected to be zero in 2024, which means that the investors will have recouped their investment and received the industry average return in VASCEPA®'s twelfth year in the market. Trial Tr. 1458:5–20 (Nicholson Direct); PDX 5-16. Over its entire lifecycle, VASCEPA® is expected to have a positive NPV of $1.9 billion, which means that it will deliver a return that exceeds the industry average by $1.9 billion. Trial Tr. 1458:21–1459:4 (Nicholson Direct); PDX 5-16.

823. Defendants' contention that VASCEPA® is not a commercial success is largely based on the theory that VASCEPA® did not make a profit in its first six years on the market. Defendants ignore the reality that drugs have long lifecycles, the beginning of which involves spending vast amounts of money on R&D. Trial Tr. 1441:15–1442:7 (Nicholson Direct); PX 612 (Grabowski 2008) at 2. Here, Amarin spent $465 million in research and development between 2008 and 2018. Trial Tr. 1426:17–24 (Nicholson Direct); PDX 5-5. Moreover, marketing spending tends to be higher at the beginning of a pharmaceutical product's lifecycle, given the need to educate physicians about the clinical profile of the new drug in question. Trial Tr. 1306:11–1307:2 (Hofmann Cross); Trial Tr. 1471:7–1472:1 (Nicholson Cross). At the same time, it can take as long as 12 years for new drugs in the top ten percent of sales to achieve peak sales. Trial Tr. 1468:11–1469:4 (Nicholson Direct); PX 607 (DiMasi 2012) at 20. Indeed, a study has shown that it took drugs 16 years on average to reach NPV of zero. Trial Tr. 1469:20–1470:7 (Nicholson Direct); PX 612 (Grabowski 2008) at 6. Therefore, the pharmaceutical industry considers the entire lifecycle of a drug in analyzing commercial success rather than just the first six years after the drug's launch. Trial Tr. 1445:23–1446:19, 1468:11–1469:4 (Nicholson Direct); 1512:17–24 (Nicholson Cross); PX 600 (Berndt 2015) at 2. Defendants' alternative approach, which relies on taking a snapshot of VASCEPA's performance *after* Amarin has incurred the vast majority of the

R&D spending but *before* it has enjoyed the fruits of that spending, is flatly contrary to industry practice.

824. Defendants also contend that Dr. Nicholson's NPV analysis is unreliable because it was excessively influenced by the one of the five forecasts upon which he relied. Defendants' contention lacks merit. The forecast in question is from a firm called H.C. Wainwright, which (as the evidence showed) does not have a history of systematically overestimating Amarin's revenue or profit. Trial Tr. 1460:22–1463:18 (Nicholson Direct); PX 752 (Wainwright Mar. 2017) at 2; PX 637 (Amarin SEC Form 10-K) at 63; PX 658 (Wainwright Feb. 2019) at 3; PX 724 (Amarin 10-Q Q1 2019) at 4. In any case, VASCEPA's NPV is expected to be positive whether or not H.C. Wainwright's forecast is included. Trial Tr. 1465:3–10 (Nicholson Direct); Trial Tr. 1504:1–16, 1521:6–18 (Nicholson Cross); DDX 8.10. This shows that Dr. Nicholson's NPV analysis is robust and reliable. Dr. Nicholson's NPV analysis is also consistent with Defendant Hikma's own January 2020 presentation to investors, which ranks VASCEPA® as having the fourth highest U.S. market size among all the drugs in Hikma's generic pipeline. PX 1218 (Hikma Presentation Jan. 2020) at 12.

825. There must be some causal relation or "nexus" between an invention and commercial success of a product embodying that invention for the evidence of commercial success to be probative of whether the invention was non-obvious. *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006). Here, there is a nexus between VASCEPA®'s commercial success and the claimed invention because the commercial success is related to the patented features (such as avoiding a rise in LDL-C) and not significantly due to other factors such as promotion, marketing, or pricing. Trial Tr. 1423:16–1424:2 (Nicholson Direct); *see also Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991) ("It is not necessary, however, that the patented invention be solely responsible for the commercial success.").

826. Amarin's marketing messages for VASCEPA conveyed the patented features of the product. Amarin's website for VASCEPA and consumer advertising described VASCEPA's clinical effectiveness in reducing TGs in patients with severe TG levels and its ability to do so

without raising LDL-C. PX 286 (VASCEPA TV Advertisement Script) at 3; PX 287 (VASCEPA Print Advertisement) at 1; PX 719 (VASCEPA Webpage) at 1. In addition, market research reports have consistently shown that VASCEPA's efficacy in reducing TG levels without increasing LDL-C levels is important to physicians when prescribing VASCEPA. Trial Tr. 1477:6–1483:7 (Nicholson Direct); PX 577 (AplusA Market Surveillance Study 2017) at 11, 41; PX 580 (ZS Associates PhysPulse Findings 2014) at 6, 28–29, 57; PX 581 (AplusA Market Surveillance Study 2016) at 8, 33.

827. The evidence also showed that the commercial success of VASCEPA was not driven by excessive marketing efforts. Companies typically vary the amount of marketing support devoted to a product over that product's life cycle. Trial Tr. 1471:7–1472:1 (Nicholson Direct). Marketing expenditures tend to be front-loaded, meaning that they tend to be high during the first few years after launch. *Id.*; Trial Tr. 1306:11–1308:11 (Hofmann Cross). VASCEPA's total marketing expenditures are substantially lower than Lovaza's throughout the first six years after the drugs' respective launches. Amarin spent approximately $20–45 million annually in marketing expenditures for VASCEPA in its first six years after launch. Trial Tr. 1472:12–21 (Nicholson Direct); PDX 5-20. In contrast, Lovaza's annual marketing expenditures ranged approximately between $70 and $140 million in its first six years after launch. Trial Tr. 1472:12–21 (Nicholson Direct); PDX 5-20. In addition, when VASCEPA's marketing-to-sales ratios are compared by year since launch with Lovaza, annual marketing-to-sales ratios for VASCEPA are in line with Lovaza's. Trial Tr. 1473:17–1474:3 (Nicholson Direct); PDX 5-21; *see also* Trial Tr. 1306:11–1308:11 (Hofmann Cross) (admitting that Lovaza was towards the end of its lifecycle in 2013).

828. The commercial success of VASCEPA is not driven by its relatively low price. VASCEPA competes with generic drugs, and a generic drug is generally cheaper than a branded drug. Trial Tr. 1305:8–1306:10 (Hofmann Cross); 1434:22–24 (Nicholson Direct). For example, in 2018, the gross price for a prescription of VASCEPA was about $320. Trial Tr. 1484:19–1485:10 (Nicholson Direct); PDX 5-22. In comparison, the gross price of generic Lovaza was about $60. Trial Tr. 1484:19–1485:10 (Nicholson Direct); PDX 5-22. Even after taking into

account rebates and discounts for VASCEPA, VASCEPA's price would still be two-and-a-half to three times higher than generic Lovaza. Trial Tr. 1485:20–1486:11 (Nicholson Direct). This shows that patients and insurers are paying a premium for the features of VASCEPA relative to generic Lovaza. *Id.*

829. Defendants' contention that the sales of VASCEPA® to patients with TGs below 500 mg/dL do not have a nexus to the claimed invention is misplaced. Given that Lovaza was being prescribed to patients with TG levels below 500 mg/dL at the time of the patented invention (around 2008), a pharmaceutical company considering whether to develop VASCEPA would have realized that obtaining approval for VASCEPA to treat severe hypertriglyceridemia would also give healthcare providers the option, in exercise of their medical judgment, to prescribe VASCEPA for patients with lower TG levels. Trial Tr. 1487:22–1489:7 (Nicholson Direct); PDX 5-23. Had the Asserted Patents been obvious, other pharmaceutical companies would have been induced by the potential for considerable sales to patients with very high and high TG levels to bring an drug equivalent to VASCEPA to market sooner. *See id.*; *see also* Trial Tr. 1424:6–15 (Nicholson Direct). Moreover, even when looking at the sales of VASCEPA to only patients with TG levels at or above 500 mg/dL, net sales have grown by a factor of six since VASCEPA's launch. Trial Tr. 1490:23–1491:16 (Nicholson Direct). Such a substantial growth in net sales over a period of six years supports VASCEPA's commercial success, even using Defendants' overly-narrow definition of relevant sales. Trial Tr. 1491:17–24 (Nicholson Direct).

830. Increased sales due to the newly approved indication based on the results of the REDUCE-IT study also have a nexus to the claimed invention. The patented invention, and FDA's approval of the patented uses of VASCEPA®, have allowed Amarin to finance and conduct the REDUCE-IT trial to demonstrate that VASCEPA® reduces the risk of cardiovascular disease. Trial Tr. 1489:8–18 (Nicholson Direct). Moreover, the newly approved indication includes patients with TGs at or above 500 mg/dL. Trial Tr. 1523:1–8 (Nicholson Cross). Therefore, there is a nexus between the increased sales resulting from the newly approved indication and the claimed invention.

831. Finally, Defendants also contend that commercial success must be apportioned between the asserted patents and the patents covering the REDUCE-IT indication. Trial Tr. 1287:17–18 (Hofmann Direct). However, there is no law that requires such apportionment for commercial success analysis.

O. Claim 1 of the '728 Patent Was Not Obvious

832. As noted above, Claim 1 of the '728 Patent is directed to a method of reducing TGs in a subject having a baseline fasting TG level of 500 mg/dL to about 1500 mg/dL, in which 4 g high purity EPA (at least 96%) is administered orally for a period of 12 weeks to a subject who does not receive concurrent lipid altering therapy, without substantially increasing LDL-C. *See supra* ¶¶ 363–364.

833. At trial, Defendants challenged this claim based on single combination of "key" prior art references—Lovaza PDR (DX 1535), Mori 2000 (DX 1538) Hayashi (DX 1532) and Kurabayashi (DX 1534). S*ee* Trial Tr. 718:20–719:3 (Heinecke Direct); *see also id.* 828:10–22 ("Q: Not only is it the key prior art, these are the four references that you used in your combinations to argue obviousness, correct? A: Correct.").

834. The Lovaza PDR, which is the 2007 prescribing information for Lovaza®, described the use of a mixture of omega-3 fatty acid esters, including both EPA and DHA, to reduce TGs in patients with severe hypertriglyceridemia. *See generally* DX 1535 (Lovaza PDR) at 2-3. As this prescribing information noted, however, Lovaza®'s reduction in TGs was accompanied by a large increase in LDL-C, and the Lovaza PDR thus warned that a patient's LDL-C levels should be monitored during therapy. *See id.* at 2-3.

835. Defendants contend that their other "key" prior art taught that it was DHA, but not EPA, that was responsible for Lovaza's increase in LDL-C—(1) Mori 2000 (DX 1538); (2) Hayashi (DX 1532); and (3) Kurabayashi (DX 1534). *See* Trial Tr. at 718:20–719:3 (Heinecke Direct)—and that this other prior art would have motivated a person of ordinary skill in March 2008 to use purified EPA to treat severe hypertriglyceridemia to avoid this rise in LDL-C, with a

reasonable expectation of success of avoiding such LDL-C increases. Trial Tr. at 759:10–760:1 (Heinecke Direct); *see also id.* at 828:23–829:22 (Heinecke Cross).

836. As the evidence showed, however, Defendants' contention is meritless, as Claim 1 of the '728 Patent was not obvious for at least the following reasons: (1) there was no reasonable expectation that high purity EPA would avoid substantial LDL-C increases in patients with severe hypertriglyceridemia; (2) DHA was thought to be better for lipid and cardiovascular effects than EPA, and a person of ordinary skill therefore would not have been motivated to eliminate substantially all DHA from Lovaza, or otherwise use high purity EPA and substantially no DHA, to treat severe hypertriglyceridemia; (3) there was neither a finite number of predictable options to pursue if seeking to lower TGs without substantially increasing LDL-C in patients with severe hypertriglyceridemia, nor a reasonable expectation of success—meaning this claim was not obvious to try; and (4) an array of objective indicia support the non-obviousness of this claim. Trial Tr. 1664:14–1778:8 (Toth Direct); *see also supra* §§ XII.G–I, N.

1. A Person of Ordinary Skill in March 2008 Would Not Have Reasonably Expected That High Purity EPA Would Avoid Substantial LDL-C Increases in Patients with Very High TGs

837. A person of ordinary skill in the art in March 2008 would not have reasonably expected that administering high purity EPA to patients with severe hypertriglyceridemia would avoid substantial rises in LDL-C. Trial Tr. 1664:21–1679:1 (Toth Direct). At the time of the invention, the prior art gave no reason to expect that any TG-lowering agent could avoid substantial LDL-C increases in severely hypertriglyceridemic patients. To the contrary, it was understood that LDL-C increases in the severely hypertriglyceridemic were a "general phenomenon" that occurred irrespective of which TG-lowering agent was used. *See supra* ¶¶ 39–53, 704–18. All approved treatments for severe hypertriglyceridemia led to dramatic increases in LDL-C in patients with very high TGs—even when such products only modestly increased (or even decreased) LDL-C in patients with lower TG levels. *See supra* ¶¶ 39–53. Moreover, a person of ordinary skill would have attributed these dramatic increases to the general mechanism through which TG-lowering medications were understood to work—through conversion of VLDL to LDL—not to any specific

medication. *See id*. A person of ordinary skill in the art at the time of the invention therefore would have expected that high purity EPA would produce large increases in LDL-C in patients with very high TGs—just as all prior approved treatments for severe hypertriglyceridemia had done. Trial Tr. 1668:8–1669:16 (Toth Direct); *see supra* ¶¶ 39–53, 704–18.

838. Other evidence from around the time of invention confirms this view. For example, in December 2008, Amarin convened an expert panel to elicit their views about the development project that led to VASCEPA®. One panelist told Amarin that "LDL-C is likely to go up as it does with virtually all [TG] lowering therapies in this group of patients [having severe hypertriglyceridemia]" and another told Amarin that it should be "very careful" about working with patients whose baseline TGs were between 500 and 650 mg/dL because they would have "relatively high IDL and therefore treatment is likely to increase the conversion of IDL to LDL in these patients—thus pushing up LDL-C." PX 754 (Expert Panel Notes) at 2; *see also* Osterloh Dep. 183:15–187:4.

839. Defendants failed to point to anything in the prior art suggesting that substantial increases in LDL-C would be avoided if high purity EPA is given to patients with very severe hyprertriglyceridemia. Defendants failed to cite, for instance, even a single prior art reference that taught that high purity EPA would perform differently with respect to LDL-C in patients with very high TGs than Lovaza or fibrates—both of which had been documented to produce large increases in LDL-C in patients with severe hypertriglyceridemia. Nor did Defendants cite any prior art teaching that one could avoid the large LDL increases observed with Lovaza in patients with very high TGs by changing the composition to include only EPA instead of Lovaza's omega-3 mixture. Trial Tr. 1665:17–1667:19 (Toth Direct).

840. Defendants' expert Dr. Heinecke even acknowledged that there was no prior art reporting the effects of high purity EPA on LDL-C in persons with severe hypertriglyceridemia. *See* Trial Tr. 800:2–5 (Heinecke Direct) ("And so I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter."); *see also* Trial Tr. 798:23–799:11 (Heinecke Direct) ("I'm

not arguing here that we know what the impact is of EPA on LDL cholesterol levels above 500 milligrams per deciliter"); Trial Tr. 832:8–20 (Heinecke Cross) ("Q. So in terms of the key prior art, there's no description of the effect of pure EPA on patients with severe hypertriglyceridemia. A. I think there is evidence that EPA would lower triglycerides in patients with high triglycerides above 500, *but there was no direct evidence on LDL cholesterol.*") (emphasis added). While Dr. Heinecke hypothesized that a person of ordinary skill would have believed that EPA would perform differently from DHA in terms of its effects on LDL-C, he did not point to any prior art suggesting that this would be the case in persons with severe hypertriglyceridemia. Trial Tr. 1668:8–1669:16 (Toth Direct). Moreover, Dr. Heinecke was unable to identify any mechanism for lowering TGs that a person of ordinary skill in March 2008 would have attributed to EPA but not DHA. Trial Tr. 864:2–865:16 (Heinecke Cross). There accordingly would have been no reason—including a reason related to mechanism of action—to expect that administering EPA by itself to a severely hypertriglyceridemic population would avoid substantially raising LDL-C when other TG-lowering agents, including Lovaza, had not. Trial Tr. 1668:24–1669:16 (Toth Direct).

841. Defendants contend that the experience with fibrates would not have informed the expectation that EPA would dramatically increase LDL-C in patients with severe hypertriglyceridemia, with Dr. Heinecke testifying that a person of ordinary skill would not have concluded that EPA had the same mechanism of action as fibrates. Trial Tr. 802:4–7 (Heinecke Direct). But the prior art specifically linked fibrates and omega-3 fatty acids when observing that, as with fibrates, omega-3 fatty acids were understood to produce large increases in LDL-C as baseline TGs increased. *See supra* ¶¶ 39–53, 704–18. And Dr. Heinecke admitted on cross-examination that there was evidence in the prior art that fibrates and omega-3 fatty acids had the *same* mechanism of action in lowering TGs: both are PPAR inhibitors (Trial Tr. 869:6-870:9 (Heinecke Cross)) and fibrates, like omega-3 fatty acids, work by enhancing the conversion of VLDL to LDL. Trial Tr. 884:2-886:10 (Heinecke Cross); PX 1027 (Goodman & Gilman 2006) at 30. Indeed, Dr. Heinecke admitted that in 2004 *FDA* stated that the mechanism by which

fenofibrate lowered TGs was the enhanced clearance of VLDL to LDL-C. Trial Tr. 880:9-883:1 (Heinecke Direct); PX 388 (Tricor Label) at 2.

842. Defendants thus fall far short of proving by clear and convincing evidence that a person of ordinary skill would have reasonably expected that high purity EPA would avoid the large rise in LDL-C observed with Lovaza and other approved TG-lowering agents in persons with very high TGs. *See supra* ¶¶ 704–18.

a) Nothing in Defendants' "key prior art" would have altered the strong expectation that highly purified EPA would produce large LDL-C increases in patients with very high TGs.

843. Lacking any prior art reporting or suggesting that high purity EPA would avoid substantial LDL-C increases *in patients with severe hypertriglyceridemia*, Defendants attempt to make do with a few small studies that administered EPA to persons with TG levels *far below* 500 mg/dL: (1) Mori 2000 (mean baseline TG level of 178 mg/dL); (2) Hayashi (mean baseline TG level of 300 mg/dL), and (3) Kurabayashi (mean baseline TG level of 136 mg/dL). *See supra* ¶¶ 549–82. Dr. Heinecke testified that because there was no substantial increase in LDL-C when EPA was administered to patients with moderately elevated or normal TGs in these smaller studies, a person of ordinary skill would have reasonably expected that the same result would occur in patients with severe hypertriglyceridemia. Trial Tr. 788:1–789:4 (Heinecke Direct). According to Dr. Heinecke, this was because "typically, if one observes effect on a value at a lower level, one anticipates seeing a similar effect at higher levels of that value." Trial Tr. 789:6–9 (Heinecke Direct).

844. But there is no reason why the person of ordinary skill would have relied on what may *typically* be the case when the prior art taught what the effect had been *specifically* when TG-lowering agents have been administered to patients with severe hypertriglyceridemia. Without exception, the prior art taught that in that specific context, the effect of TG-lowering agents on LDL-C depended upon the baseline TG levels of the patient population, and that severely hypertriglyceridemic patients would experience large LDL-C increases even when persons with lower TGs did not. *See supra* ¶¶ 39–53; *see also* Trial Tr. 1667:11–1668:7 (Toth Direct)). And the

prior art reported that with TG-lowering agents—including omega-3 fatty acids—"the higher the baseline triglyceride level, the greater these lipids [including LDL-C] may be increased." PX 923 (McKenney I) at 5; Trial Tr. 1590:12–1595:3 (Toth Direct). A person of ordinary skill therefore would not have understood the references in Defendants' "key prior art" involving administration of EPA to patients with normal to moderately elevated TG levels to be informative about what the effect on LDL-C would be in severely hypertriglyceridemic patients. Trial Tr. 1574:3–1598:3, 1665:17–1669:16, 1716:15–1717:2 (Toth Direct). Instead, such a person would have expected EPA to raise LDL-C dramatically in patients with very high TGs—as was the case with the prior approved treatments for severe hypertriglyceridemia. Trial Tr. 1574:3–1598:3, 1665:17–1669:16, 1716:15–1717:2, 1718:13–1722:6 (Toth Direct); *see also supra* ¶¶ 39–53.

b) The Epadel Prescribing Information 2007 would not have provided a reasonable expectation of avoiding large LDL-C increases in patients with very high TGs.

845. In his testimony, Dr. Heinecke also discussed the Epadel Prescribing Information 2007. Trial Tr. 747:5–24 (Heinecke Direct). An extensive discussion of this reference is set forth above. *See supra* ¶¶ 586–94.

846. The Epadel Prescribing Information did not address patients with severe hypertriglyceridemia. *See supra* ¶¶ 586–94. The Epadel Prescribing Information 2007 did not report the LDL-C effects of purified EPA in any population, let alone in patients with very high triglycerides. DX 1528 (Epadel PI 2007); Trial Tr. 1676:2–6 (Toth Direct) Trial Tr. 800:2–5 (Heinecke Direct) ("And so I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter."); *see also* Trial Tr. 798:23–799:11 (Heinecke Direct).

847. Having not clearly described administration of high purity EPA to patients with severe hypertriglyceridemia, nor recited any LDL-C effects in any population, nothing about the Epadel Prescribing Information 2007 would have provided a reasonable expectation of success in avoiding LDL-C increases in patients with severe hypertriglyceridemia with administration of high purity EPA.

c) Other prior art on purified EPA would not have provided a reasonable expectation of avoiding substantial increases in LDL-C

848. Dr. Heinecke also discussed some other references involving high purity EPA—Takaku 1991 (DX 1550), Nakamura 1999 (DX 1539), Matsuzawa 1991 (DX 1537), and Saito 1998 (DX 1546)—in which a single subject or a few subjects had TG levels of at least 500. Trial Tr. 756:6–15 (Heinecke Direct). As discussed extensively above, none of these references addressed patient *populations* with severe hypertriglyceridemia, and none would have provided a POSA with a reasonable expectation of success in avoiding LDL-C increases in patients with severe hypertriglyceridemia. *See supra* ¶¶ 612–20; *see also* Trial Tr. 1669:20–1673:22 (Toth Direct). Indeed, none of these references reported the LDL-C effects of high purity EPA in patients with severe hypertriglyceridemia, nor did any study the effect of a 4g dose of high purity EPA. *See supra* ¶¶ 612–20; Trial Tr. 1670:1–1673:22 (Toth Direct).

849. Nor would Yokoyama (DX 1553) or other art concerning the JELIS trial have altered the strong expectation that administration of high purity EPA would dramatically increase LDL-C in patients with severe hypertriglyceridemia. The subjects in JELIS had a median baseline TG level of 153 mg/dL (1.73 mmol/L). DX 1553 (Yokoyama 2007) at 3, Tbl. 1; Trial Tr. 1744:24–1745:15 (Toth Direct). These patients had TG levels that were barely above normal, and there is no indication that any of the JELIS population had TG levels of at least 500 mg/dL. Trial Tr. 1744:2-1745:15 (Toth Direct); Trial Tr. 1120:7–12 (Fisher Cross). Therefore JELIS would have told a person of ordinary skill nothing about the LDL-C effects of EPA in patients with severe hypertriglyceridemia. *See supra* ¶ 622; *see also* Trial Tr. 1745:6–21 (Toth Direct).

d) Documents Reflecting Amarin's Views of the Prior Art Would Not Have Provided a Person of Ordinary Skill in the Art with a Reasonable Expectation of Success in Avoiding LDL-C Increases in Patients with Severe Hypertriglyceridemia

850. Defendants also repeatedly pointed to statements made by Amarin and the inventors regarding the prior art and the effects that the inventors and Amarin expected purified EPA to have on LDL-C in severely hypertriglyceridemic patients. *See, e.g.*, Trial Tr. 1830:12–1831:23 (Toth

Cross). Defendants contend that such statements are evidence that there would have been a reasonable expectation of success in avoiding LDL-C increases in patients with very high TGs. They are mistaken.

851. As detailed extensively above, Defendants' reliance on Amarin statements is misplaced. According to the Federal Circuit, whose case law is controlling here, the thoughts of an inventor are not relevant to the obviousness inquiry. Rather, the relevant inquiry is what a person of *ordinary skill* would have believed: "The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm. Co.*, 678 F.3d at 1296. "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art *that existed at the time*. The invention must be evaluated *not through the eyes of the inventor*, who may have been of exceptional skill, but as by one of 'ordinary skill'." *Interconnect Planning Corp*, 774 F.2d at 1138 (emphasis added); *see also Standard Oil Co*, 774 F.2d at 454 ("The statutory emphasis [of the obviousness inquiry] is on a person of *ordinary* skill. Inventors, as a class, . . . possess something—call it what you will—which sets them apart from the workers of *ordinary* skill, and one should not go about determining obviousness under § 103 by inquiring into what *patentees* (*i.e.*, inventors) would have known or would likely have done, faced with the revelations of references.").

852. Relying on the inventors' statements would therefore constitute clear and reversible error. So too would relying more generally on Amarin internal statements about the likely effects of EPA. As of March 2008, when the invention was conceived, Amarin was a tiny company of approximately a dozen employees, Trial Tr. 278:11–17 (Ketchum Direct), and Amarin as a whole had already been exposed to the views and insights of the inventors. Indeed, when providing information to his colleagues at Amarin, Dr. Manku was not only communicating with his fellow scientists—like Dr. Ian Osterloh—but was also communicating with business-focused individuals like Stuart Sedlack. *See, e.g.*, PX 472 (Mar. 24, 2008 M. Manku E-mail) at 1 (describing his views on how EPA affects certain biomarkers to Dr. Ian Osterloh, Stuart Sedlack and others); Manku

Dep. 147:11–17 (describing the March 24, 2008 e-mail as him "trying to bring to [my colleagues'] attention what my thoughts are about – and they are asking me questions and I am replying to their questions with my thoughts."); *see also* Manku Dep. 186:3–8 (explaining that Stuart Sedlack "was in charge of business development.").

853. Moreover, statements by Amarin employees predicting how purified EPA would affect TGs and LDL-C levels in severely hypertriglyceridemic patients track the statements Dr. Manku made when attempting to convince his colleagues that purified EPA would not increase LDL-C in these patients. *See* PX 475 (Mar. 16, 2008 M. Manku E-mail) at 1. Moreover, Mr. Sedlack, the custodian of a March 2008 internal Amarin document that Defendants cite, relied on Dr. Manku's technical knowledge EPA's biochemical effects. *See* PX 472, (Mar. 24, 2008 M. Manku E-mail) at 1 (explaining to the Amarin team Dr. Manku's belief that EPA would not increase LDL and would have other beneficial effects on cardiovascular biomarkers). Consequently, it is improper to read the prior art references in this case in view of Amarin internal documents, which interpret the prior art references "through the lens of what [Amarin and the inventors] had invented." *Neptune Generics*, 921 F.3d at 1377. A fuller discussion of Amarin some of the particular Amarin statements on which Defendants improperly rely is set forth above. *See supra* ¶¶ 744–54.

2. A POSA Would Not Have Been Motivated to Eliminate the DHA from Lovaza so as to Arrive a High Purity EPA Formulation for Treatment of Severe Hypertriglyceridemia

854. Defendants' obviousness case also fails because they have not demonstrated by clear and convincing evidence that a person of ordinary skill would have been motivated to use high purity EPA and substantially no DHA to treat severe hypertriglyceridemia—a critical element of establishing obviousness of the Asserted Claims, including Claim 1 of the '728 Patent. *See supra* ¶¶ 668–703; *see also* Trial Tr. 1639:3–1703:7 (Toth Direct)).

855. Defendants contend that a person of ordinary skill in March 2008 would have been motivated to modify Lovaza—which contains a mixture of EPA and DHA (and other naturally occurring omega-3 fatty acids)—to achieve a treatment for severe hypertriglyceridemia that avoids

large increases in LDL-C. But nothing in the prior art, including Defendants' "key prior art," would have motivated a person of ordinary skill to do so. To the contrary, the prior art, including the very Mori 2000 reference upon which Defendants rely, expressly taught that *DHA* was the superior therapeutic agent. *See supra* ¶¶ 553–63, 673–85. Moreover, nothing in the prior art taught that EPA would provide an advantage over DHA with respect to LDL-C in *any population*—let alone in a population of severe hypertriglyceridemic patients. Rather, even in patients with TGs below 500 mg/dL, the prior art as a whole taught that *both* DHA and EPA raised LDL-C. *See supra* ¶¶ 684–91. Given that the prior art taught that DHA had several therapeutic advantages over EPA, and that EPA had no advantages over DHA, a person of ordinary skill would not have been motivated to eliminate DHA from Lovaza or otherwise arrive at a high purity EPA formulation for the treatment of severe hypertriglyeridemia. *See supra* ¶¶ 673–96. Consequently, Defendants have failed to prove motivation to arrive at the claimed invention by clear and convincing evidence.

856. A fuller discussion of why a person of ordinary skill in the art would not have been motivated to eliminate substantially all DHA from Lovaza, or otherwise pursue a high purity EPA formulation for treatment of severe hypertriglyceridemia, is set forth above, and fully incorporated herein. *See supra* ¶¶ 668–703.

3. It Was Not "Obvious to Try" 4 g High Purity EPA with Substantially No DHA in Patients with TGs of at Least 500 mg/dL

857. Defendants also contend that it would have been at least "obvious to try" 4g high purity EPA as a treatment for severe hypertriglyceridemia. As explained above, however, the evidence established the opposite. *See supra* ¶¶ 720–25.

858. As Defendants acknowledge, to prove that an invention was "obvious to try," a patent challenger must provide, *inter alia*, that there is a finite number of identified predictable solutions to that problem." Trial Tr. 760:2–11 (Heinecke Direct); *see also supra* ¶¶ 514–15. While Defendants focus on Lovaza, and argue that there were only three options when assessing its effects on LDL-C—either the DHA, the EPA, or both were responsible for the increase in LDL-C in patients were severe hypertriglyceridemia, *see* Trial Tr. 760:2–761:5 (Heinecke Direct)—they

focus on the wrong question, and one that smacks of hindsight. The real question is whether the person of ordinary skill in the art trying to avoid a substantial increase in LDL-C in that population group would have identified only three options and would have been able to predict that those options would solve that problem. Trial Tr. 1706:8–1708:12 (Toth Direct).

859. A person of ordinary skill in the art would not have reasonably expected that *any* option would avoid substantial increases in LDL-C in patients with severe hypertriglyceridemia, given that such increases were understood to be a "general phenomenon" resulting from the mechanism by which TG-lowering agents, including omega-3 fatty acids, lowered TGs—by converting VLDL to LDL. *See supra* ¶¶ 39–53. Instead, the person of ordinary skill would have expected that any omega-3 fatty acid formulation, including both pure DHA and EPA, would dramatically increase LDL-C in persons with severe hypertriglyceridemia. *See supra* ¶¶ 39–53.

860. Moreover, a person of ordinary skill in March 2008 seeking to arrive at an improved treatment for severe hypertriglyceridemia that avoided LDL-C increases would have had numerous potential options to pursue, including trying to develop a new niacin or fibrate product, a combination of existing agents, or some new type of TG-lowering agent altogether. Trial Tr. 1707:1–1708:12 (Toth Direct). And even if one had been limited to fish oil formulations, there would have been a vast array of choices to pursue, as one could have varied the ratio between the principal omega-3 fatty acids (in a wide variety of ratios),[27] could have varied the dose, or could have considered adding other substances, such as alpha-linolenic acid (as some people had), omega-6s, or omega-9s. Trial Tr. 1707:13–1708:9 (Toth Direct). The list was potentially infinite. *Id.*

[27] Around the time of the claimed invention, and even in the years following, researchers continued to pursue omega-3 mixtures in a variety of ratios of EPA and DHA. The clinical trials underway as of 2008 all investigated formulations that included substantial amounts of DHA, including the OMEGA trial (460 mg EPA/380 mg DHA); ALPHA OMEGA (400 mg EPA-DHA); SU.FOL.OM3 (400 mg EPA/200 mg DHA); ORIGIN (465 mg EPA/375 mg DHA); R&P (500 mg EPA/500 mg DHA); DO-IT (1150 mg EPA/800 mg DHA); ASCEND (460 mg EPA/380 mg DHA). *See supra* ¶¶ 142–51. Dr. Fisher himself admitted that, as of 2008, a variety of trials on a variety of mixtures of EPA and DHA were being conducted. Trial Tr. 1183:13–16 (Fisher Cross).

861. Among such choices, it would not have been obvious to administer 4 g/day of highly purified EPA with substantially no DHA, given all of the advantages the prior art reported for DHA, as well as the fact that EPA raised potential concerns about fasting glucose levels in diabetics, who make up a large portion of persons with very high triglycerides. *See supra* ¶¶ 553–63, 673–85. Nor would a person of ordinary skill in the art have seen an LDL-C advantage with using purified EPA. *See supra* ¶¶ 683–91.

862. Real world evidence confirms that it would not have been obvious to try a composition of high purity EPA with substantially no DHA to treat severe hypertriglyceridemia. Although purified EPA had been known since at least the approval of Epadel in the early 1990s, no one as of March 2008 had developed a method of lowering TGs in the severely hypertrigylyceridemia population using a composition of highly purified EPA and substantially no DHA. Trial Tr. 889:1–890:1 (Heinecke Cross). Here, the "elapsed time between the prior art and the [asserted patents'] filing date evinces that the [claimed invention] was not obvious to try." *Leo Pharm. Prod.*, 726 F.3d at 13456.

863. That the clinical advantages of purified EPA in treating severe hypertriglyceridemia were not obvious from the prior art is manifest from the fact that GSK and Reliant developed the Lovaza omega-3 mixture—rather than high purity EPA—in 2004 to treat severe hypertriglyceridemia. Trial Tr. 889:1–19 (Heinecke Cross). Had the benefits of using purified EPA over the mixture in treating severe hypertriglyceridemia been obvious, GSK and its predecessors would not have pursued the mixture instead.

4. Objective Indicia Further Supports the Non-Obviousness of Claim 1 of the '728 Patent

864. The evidence established that several objective indicia support the non-obviousness of the Asserted Claims, including claim 1 of the '728 Patent. Some of these objective indicia relate to the MARINE trial, while others relate to the REDUCE-IT trial. *See supra* § XII.N. These objective indicia, which apply to all Asserted Claims, are set forth extensively above, along with a discussion of why there is a nexus between the objective indicia and the Asserted Claims. *See*

supra § XII.N. These objective indicia include unexpected benefits, satisfaction of long-felt needs, skepticism, praise, and commercial success. *See supra* § XII.N.

P. Claim 16 of the '728 Patent Was Not Obvious

865. Claim 16 of the '728 Patent depends from, and incorporates the elements of, Claim 1 of the '728 Patent, but requires that the pharmaceutical composition comprises no fatty acid, other than ethyl-EPA, in a quantity that is more than 0.6% by weight of all fatty acids combined. *See* PX 21 ('728 Patent) at 22. By contrast, Claim 1 of the '728 Patent requires that the pharmaceutical composition comprise at least about 96% by weight of all fatty acids present EPA, and substantially no DHA or its esters—*i.e.*, no more than about 4% DHA or its esters. *See id.* Claim 16 thus requires even less DHA than Claim 1. *See id.*

866. Defendants challenge Claim 16 of the '728 Patent over the same references and same rationale as Claim 1 of the '728 Patent—Lovaza PDR, Mori 2000, Kurabayashi, and Hayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross). Defendants further contend that the additional limitation specifying that the composition comprise no fatty acid other than EPA in a quantity that is more than about 0.6% by weight of all fatty acids combined is disclosed in WO '900, which described among numerous possible formulations a formulation that had less than 0.1 percent DHA (though Dr. Heinecke did not rely on WO '900, which contains no discussion of severe hypertriglyceridemia for *clinical* guidance). *See supra* ¶¶ 583–85; *see also* Trial Tr. 769:20–770:16 (Heinecke Direct); DX 1525 (WO '900) at 16.

867. Claim 16 of the '728 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* § XII.O; *see also* Trial Tr. 1778:9–13 (Toth Direct). Those reasons include that (1) nothing in the prior art, including the references in Defendants' obviousness combination, would have altered the strong expectation that highly purified EPA would produce large LDL-C increases in individuals with severely elevated TG levels, and therefore would not have provided a reasonable expectation that one could reduce TGs without substantially and significantly increasing LDL-C in persons with TG levels of at least 500 mg/dL; (2) the references in Defendants' obviousness combination, as well as the prior art as a whole,

would not have motivated a person of ordinary skill to eliminate substantially all DHA and use highly purified EPA and substantially no DHA, which means that such a person would not have been led to a formulation with no more than 0.6% by weight DHA; (3) it would not have been "obvious to try" 4 g highly purified EPA with substantially no DHA as a method of lowering TGs in patients with severe hypertriglyceridemia without adversely affecting LDL-C levels; and (4) objective indicia reinforce the non-obviousness of the claim.

Q. Claim 14 of the '715 Patent Was Not Obvious

868. Defendants challenge Claim 14 of the '715 Patent over the same references as Claim 1 of the '728 Patent—Lovaza PDR, Mori 2000, Kurabayashi, and Hayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross). This claim covers the same general method as Claim 1 of the '728 Patent but specifies that the method is administered to effect a statistically significant reduction in TGs and apo B without effecting a statistically significant increase in LDL-C. *See* PX 22 ('715 Patent) at 22.

869. Claim 14 of the '715 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* § XII.O; *see also* Trial Tr. 1778:9–13 (Toth Direct). Those reasons include that (1) nothing in the prior art, including the references in Defendants' obviousness combination, would have altered the strong expectation that highly purified EPA would produce large LDL-C increases in individuals with severely elevated TG levels, and therefore would not have provided a reasonable expectation that one could reduce TGs without substantially and significantly increasing LDL-C in persons with TG levels of at least 500 mg/dL; (2) the references in Defendants' obviousness combination, as well as the prior art as a whole, would not have motivated a person of ordinary skill to eliminate substantially all DHA and use highly purified EPA and substantially no DHA; and (3) it would not have been "obvious to try" 4 g highly purified EPA with substantially no DHA as a method of lowering TGs in patients with

severe hypertriglycreidemia without adversely affecting LDL-C levels; (4) objective indicia reinforce the non-obviousness of the claim.[28]

870. Claim 14 of the '715 Patent was also not obvious for the additional reason that it would not have been obvious that administration of 4 g per day of high purity EPA would effect a statistically significant reduction in apo B in persons with severe hypertriglyceridemia. *See* Trial Tr. 1778:14–1780:22 (Toth Direct). As noted above, a person of ordinary skill in the art would have based her expectation about the effect of high purity EPA on the experience with Lovaza, which did not show a statistically significant reduction in apo B in patients with severe hypertriglyceridemia. *See supra* ¶¶ 659–63, 719; *see also* Trial Tr. 1778:14–1779:9 (Toth Direct).

871. Defendants attempt to rely upon Kurabayashi (DX 1534), Grimsgaard (DX 1530), and Nozaki (DX 1541) to teach this apo B limitation, but none of those references disclosed that administration of highly purified EPA produces statistically significant reductions in apo B in patients with severe hypertriglyceridemia. Trial Tr. 1779:25–1780:22 (Toth Direct). Kurabayashi administered a combination of estriol and EPA to patients with a mean TG level of 136 mg/dL, which is not elevated. *See supra* ¶¶ 578–82. Grimsgaard administered EPA to patients with mean TG level of 1.23 mmol/L, which is far below the 5.65 mmol/L benchmark that corresponds to 500 mg/dL. DX 1530 (Grimsgaard) at 5, Tbl. 4; DX 1531 (Harris 1997) at 1. And in Nozaki, the average baseline TG level was only 165 mg/dL, which is only slightly above normal. *See* DX 1541 (Nozaki) at 5, Tbl. II. Nowhere did Dr. Heinecke or defendants cite prior art demonstrating the effect of apo B in persons with severe hypertriglyceridemia. Trial Tr. 1780:19–22 (Toth Direct). Moreover, another prior art reference that Dr. Heinecke discussed in his direct examination reported that, in patients with TGs below 500 mg/dL, EPA increased apo B by 16.7% by the end

[28] Claim 14 uses a somewhat different LDL-C term than Claim 1 of the '728 Patent, specifying that the method does not "effect [] a statistically signficant increase of [LDL-C] in the subject." PX 22 ('715 Patent) at 22. This difference has no effect on the analysis. Trial Tr. 1782:2-9 (Toth Direct). Nor do the other variations on the LDL-C term in the other Asserted Claims. *See* Trial Tr. 1782:2-20 (Toth Direct).

of the study. *See* DX 1550 (Takaku) at 21 (reporting a 16.7% increase in apo B after one year of EPA administration).

872. In addition, as noted above, Kurabayashi did not study the effect of EPA alone, but instead looked at the effect of a combination of EPA and estriol (a lipid-altering agent) on lipid parameters of Japanese post-menopausal women with triglycerides below 500 mg/dL. *See supra* ¶¶ 578–82. Because Kurabayashi did not study the effect of EPA alone, a person of ordinary skill in the art would not have been able to discern the effect that EPA had on apo B, even in the population that Kurabayashi studied.

R. Claim 1 of the '677 Patent Was Not Obvious

873. Like Claim 1 of the '728 Patent, this claim covers a method of administering high purity EPA to effect a reduction in triglycerides in a subject with severe hypertriglyceridemia without substantially increasing LDL-C. *See* PX 25 ('677 Patent) at 21. Defendants challenge this claim over the same references as Claim 1 of the '728 Patent—Lovaza PDR, Mori 2000, Kurabayashi, and Hayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross). This claim was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* § XII.O; *see also* Trial Tr. 1778:9–13, 1782:2–15 (Toth Direct).

874. Claim 1 of the '677 Patent differs from Claim 1 of the '728 Patent in that it does not prohibit a patient from using concurrent lipid altering therapy. *See* PX 25 ('677 Patent) at 21. Prior to the last day of trial, Defendants never contended that this difference was of any relevance to their obviousness case, but during the cross examination of the case's final witness, Dr. Toth, Defendants appeared to try to lay the groundwork for a new theory based on new references. Ostensibly recognizing that they cannot show a reasonable expectation of success in avoiding LDL-C increase in patients with severe hypertriglyceridemia with EPA *alone*, Defendants suggested during the cross-examination of Dr. Toth that because Claim 1 of the '677 Patent allows for the concurrent administration of a lipid altering therapy, one could reasonably expect to avoid the substantial LDL-C increase if EPA were *co-administered with a statin*. *See* Trial Tr. 1883:11–1884:22, 1890:17–1894:2 (Toth Cross).

875. Defendants should not be entitled to change their contentions during the cross examination of the case's final witness. But even if permitted, this new theory would not help Defendants.

876. The purported motivation that Defendants have offered for why a person of ordinary skill would have wanted to modify Lovaza is to avoid the need to co-administer a statin. *See* Trial Tr. 813:8–19 (Heinecke Direct) ("Q: Even though LDL-C could be reduced with statins, was there still a motivation to improve Lovaza to avoid increases in LDL-C? A: Yes, there is. Obviously patient compliance is a major issue in clinical medicine. For example, most patients prescribed statins don't take them after six months. . . . It's clearly easier to take one pill, for example, of pure EPA to treat a condition than to combine two pills such as Lovaza with a statin."). Thus, under Defendants' theory, the question whether a person of ordinary skill would have been motivated to pursue EPA rests on whether she would have reasonably expected success in avoiding LDL-C increases *without a statin*. If not, there would have been no reason to pursue high purity EPA, or to change Lovaza. Thus, Defendants' obviousness theory rests on whether a person of ordinary skill would have reasonably expected to avoid large increases in LDL-C in severely hypertriglyceridemic patients with EPA alone—whether or not the Asserted Claims specifically prohibit statin use.

877. *Second*, Defendants' ostensible new theory also fails to establish motivation to co-administer a statin with *high purity EPA*. As noted above, the prior art taught that DHA had advantages over EPA, so a person of ordinary skill would have seen no reason to use a formulation with *high purity EPA* and substantially no DHA, even if they were going to combine an omega-3 fatty acid with a statin. *See supra* ¶¶ 553–63, 673–81.

878. *Third*, the Asserted Claims require that the purified EPA be administered with the expectation that *it* will not raise LDL-C while reducing TGs in severe hypertriglyceridemia patients. Whether that rise can be negated through some other agent, such as a statin, is a separate question—and cannot be used in trying to make the case that there would have been a reasonable

expectation of avoiding LDL-C increases with EPA by itself when administered to severely hypertriglyceridemic patients.

879. In any event, there would have been no reasonable expectation of avoiding LDL-C increases in patients with severe hypertriglyceridemia, even if high purity EPA were co-administered with a statin. A person of ordinary skill would have been aware of no data showing that co-administration of a statin with EPA would negate the anticipated and large LDL-C increases in patients with severe hypertriglyceridemia—and Defendants cited none.

880. On cross examination, Defendants attempted to make do with data from a version of the Lovaza prescribing information showing that co-administration of a statin in patients with TGs of *200 to 499* mg/dL resulted in a 3.5% increase in LDL-C compared to placebo. DX 1578 (Lovaza Prescribing Information) at 1; Trial Tr. 1872:13–1873:2 (Toth Cross); *see also* Trial Tr. 1957:10–23 (Toth Re-Direct). Defendants implied that a person of ordinary skill would have understood that, in view of this data, use of a statin would completely negate the large LDL-C increases expected in severe hypertriglyceridemia patients with EPA. DX 1578 (Lovaza Prescribing Information) at 1, Tbl.1; *see also* Trial Tr. at 1872:13–1873:2 (Toth Cross).

881. But the prior art showed that increases in LDL-C were dramatically greater in patients with TGs of at least 500 mg/dL compared to patients with TGs below 500 mg/dL. *See supra* ¶¶ 39–53. Consequently, a person of ordinary skill in the art would not have understood that statins could negate the much larger LDL-C increases that would have been anticipated in patients with *severe hypertriglyceridemia*.

882. Defendants may cite snippets of Dr. Toth's testimony in an attempt support their theory that statins "could" prevent LDL-C increases in patients with severe hypertriglyceridemia. Trial Tr. at 1874:10–15 (Toth Cross) ("It could. I would qualify it with the word 'could.'"). But Dr. Toth testified that whether one could negate the LDL-C elevation would depend upon the "magnitude of the elevation" and the "baseline TG level." Trial Tr. at 1879:9–15 (Toth Cross). And Defendants point to no data or prior art reference teaching that with the typical magnitude of LDL-C elevation in patients with very high TGs, statins could negate the rise in LDL-C. *See supra*

¶¶ 731–34. Thus, even if Defendants were permitted to raise their new theory, it would fall far short of the clear and convincing evidence required to prove obviousness.

883. Claim 1 of the '677 Patent also differs from Claim 1 of the '728 Patent in that the lipid effects in Claim 1 of the '677 Patent are compared to placebo control, rather than a second subject who has not received the pharmaceutical composition. *Compare* PX 21 ('728 Patent) at 21 *to* PX 25 ('677 Patent) at 21. But this difference in claim language makes no material difference to the analysis, as it would not have been obvious that the claimed method of 4g high purity EPA would lower TGs in subjects with severe hypertriglyceridemia without substantially increasing LDL-C in either case. *See* Trial Tr. 1781:21–1782:20 (Toth Direct).

S. Claim 8 of the '677 Patent Was Not Obvious

884. Claim 8 of the '677 Patent incorporates the elements of Claim 1 of the '677 Patent, but adds the limitation that the method of claim 1 effects "a reduction in apolipoprotein B compared to placebo control." PX 25 ('677 Patent) at 22. Defendants challenge this claim over the same references as Claim 1 of the '677 Patent—Lovaza PDR, Mori 2000, Hayashi, and Kurabayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross).

885. Claim 8 of the '677 Patent was not obvious for the same reasons that Claim 1 of the '677 Patent was not obvious (which in turn was not obvious for the same reasons that Claim 1 of the '728 was not obvious). *See supra* §§ XII.O, XII.R ; *see also* Trial Tr. at 1778:9–13 (Toth Direct), 1778:14–1780:22 (Toth Direct).

886. In addition, for the same reasons as discussed above in connection with Claim 14 of the '715 Patent, it was not obvious to administer 4 g of high purity EPA (at least 96% by weight of all fatty acids present) and substantially no DHA to reduce apo B. *See supra* ¶¶ 870–72.

887. The language of Claim 8 of the '677 Patent differs from Claim 14 of the '715 Patent, but this does not materially affect the obviousness analysis. Claim 8 of the '677 Patent specifies that the reduction in apo B be in comparison to a placebo control rather than a second subject. *See* PX 025 ('677 Patent) at 22. It would not have been obvious that the claimed method of high purity

EPA would lower apo B in a subject with severe hypertriglyceridemia, whether by comparison to a placebo control or a second subject. *See* Trial Tr. 1778:14–1780:22 (Toth Direct).

T. Claim 1 of the ’652 Patent Was Not Obvious

888. Like Claim 1 of the ’728 Patent, this claim covers a method of administering high purity 4g EPA to effect a reduction in TGs in a subject with severe hypertriglyceridemia without substantially increasing LDL-C. *See* PX 026 (’652 Patent) at 22. Defendants challenge this claim over the same references as Claim 1 of the ’728 Patent—Lovaza PDR, Mori 2000, Hayashi, and Kurabayashi, and for the same reasons. *See* Trial Tr. 828:10–22 (Heinecke Cross).

889. Claim 1 of the ’652 Patent was not obvious for the same reasons that Claim 1 of the ’728 Patent was not obvious. *See supra* § XII.O; *see also* Trial Tr. at 1778:9–13 (Toth Direct), 1781:21–1782:20 (Toth Direct). The language of Claim 1 of the ’652 Patent differs from Claim 1 of the ’728 Patent in a couple of respects, but neither materially affects the obviousness analysis. First, in contrast to Claim 1 of the ’728 Patent, Claim 1 of the ’652 Patent is silent on whether the subject receiving the pharmaceutical composition receives a concurrent lipid altering therapy. *See* PX 26 (’652 Patent) at 22. For the reasons discussed in connection with Claim 1 of the ’677 Patent, whether or not a claim prohibits the use of a statin is immaterial to the obviousness analysis. *See supra* ¶ 874–82. Therefore, Claim 1 of the ’652 Patent would not have been obvious to a person of ordinary skill in the art, and regardless of whether the subject was on concurrent lipid altering therapy.

890. Second, the lipid effects in Claim 1 of the ’652 Patent are compared to baseline, whereas the lipid effects in Claim 1 of the ’728 Patent are compared to a second subject who has not received the pharmaceutical composition. *Compare* PX 21 (’728 Patent) at 21 *to* PX 026 (’652 Patent) at 22. But this difference in claim language does not affect the obviousness analysis because it would not have been obvious that the claimed method of administering 4 g high purity EPA would lower TGs in severe hypertriglyceridemia patients without substantially increasing LDL-C, whether by comparison to baseline or a second subject not receiving the pharmaceutical composition. *See* Trial Tr. 1781:21–1782:20 (Toth Direct).

U. Claim 4 of the ’560 Patent Was Not Obvious

891. Like Claim 1 of the ’728 Patent, this claim covers a method of reducing TGs in a subject having a fasting baseline TG level of 500 mg/dL to about 1500 mg/dL using high purity EPA. *See* PX 30 (’560 Patent) at 23. Claim 4 of the ’560 Patent adds the limitation that the method effects “a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5%.” *Id.*. Defendants challenge this claim over the same references as Claim 1 of the ’728 Patent—LOVAZA® PDR, Mori 2000, Hayashi, and Kurabayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross). Defendants contend that the additional limitation that the method reduces TGs by about 10% without increasing LDL-C by more than 5% is disclosed in Mori 2000. *See* Trial Tr. 775:2–12 (Heinecke Direct).

892. Claim 4 of the ’560 Patent was not obvious for the same reasons that Claim 1 of the ’728 patent was not obvious. *See supra* § XII.O; *see also* Trial Tr. 1778:9–13, 1781:21–1782:20 (Toth Direct).

893. In addition, Mori 2000 does not disclose the additional limitation of Claim 4 of the ’560 Patent that the method reduce triglycerides by at least 10% without increasing LDL-C by more than 5% in a subject with very high triglycerides. As discussed above, Mori 2000 is not directed to, and does not describe, LDL-C effects in persons with TGs of at least 500 mg/dL. *See supra* ¶¶ 549–52. Therefore, it does not disclose a method that does not increase LDL-C by more than 5% in patients with severe hypertriglyceridemia. Moreover, as discussed above, a person of ordinary skill would have expected that administering high purity EPA would dramatically increase LDL-C in persons with severe hypertriglyceridemia, well in excess of a mere 5%. *See supra* ¶¶ 39–53, 704–18.

894. There are some differences in claim language between Claim 4 of the ’560 Patent and Claim 1 of the ’728 Patent:

- The high purity EPA composition of Claim 4 of the ’560 Patent cannot contain more than 3% DHA, whereas the composition of Claim 1 of the ’728 Patent has “substantially no DHA”—*i.e.*, no more than 4% DHA—and at least 96% EPA of all fatty acids present; and

- Claim 4 of the ’560 patent requires administering 4 capsules, each capsule comprising about 900 mg to about 1 g, whereas Claim 1 of the ’728 Patent specifies a daily dose of about 4 g.

See PX 21 (’728 Patent) at 22; PX 30 (’560 Patent) at 23.

895. These differences are not material to the obviousness analysis. That Claim 4 of the ’560 Patent requires that the composition include even less DHA than Claim 1 of the ’728 Patent (no more than 3% versus no more than 4% DHA) does not change the conclusion that the claim would not have been obvious, given that a person of ordinary skill in the art would have understood that DHA provided several therapeutic advantages, and therefore would have wanted to include DHA in substantial amounts. *See supra* § XII.G; *see also* Trial Tr. at 1781:21–1782:20 (Toth Direct). Thus, just as a person of ordinary skill would have wanted to pursue a composition with DHA far in excess of 4%, so too that person would have wanted to pursue a composition containing DHA far in excess of 3%.

896. In addition, the fact that Claim 4 of the ’560 Patent requires that the composition be administered in 4 capsules per day, each capsule comprising about 900 mg to about 1 g of EPA, as opposed to 4 g per day of high purity EPA, is not material to the obviousness analysis either, as a 3.6–4 g/day dosage given in 4 capsules would not have been obvious for the same reasons that a 4 g/day dose of high purity EPA would not have been obvious. *See* Trial Tr. 1780:23–1781:9 (Toth Direct).

V. Claim 17 of the ’560 Patent Was Not Obvious

897. Claim 17 of the ’560 Patent covers the same method as Claim 4 of the ’560 patent except that the TG reduction is compared to placebo control. *See* PX 30 (’560 Patent) at 23. Defendants challenge Claim 17 of the ’560 Patent over the same references as Claim 4 of the ’560 Patent—Lovaza PDR, Mori 2000, Hayashi, and Kurabayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross).

898. Claim 17 of the ’560 Patent was not obvious for the same reasons that Claim 4 of the ’560 Patent was not obvious (which, in turn, was not obvious for the same reasons that Claim 1 of the ’728 Patent was not obvious). *See supra* §§ XII.O, XII.U; *see also* Trial Tr. at 1778:9–13

(Toth Direct). The addition of "compared to placebo control" does not materially affect the obviousness analysis because it would not have been obvious that the claimed method of high purity EPA would lower TGs in a subject with severe hypertriglyceridemia without increasing LDL-C, whether or not the effects were compared to placebo control. *See* Trial Tr. 1781:21–1782:20 (Toth Direct).

W. Claim 1 of the '929 Patent Was Not Obvious

899. Like Claim 1 of the '728 Patent, this claim covers a method of administering about 4 g high purity EPA and substantially no DHA (not more than about 4%) to reduce TGs. But unlike Claim 1 of the '728 Patent, Claim 1 of the '929 Patent lacks a limitation requiring that the method avoid a substantial increase in LDL-C. *See* PX 31 ('929 Patent) at 31–32. Defendants challenge Claim 1 of the '929 Patent over the same references as Claim 1 of the '728 Patent—Lovaza PDR, Mori 2000, Hayashi, and Kurabayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross).

900. Claim 1 of the '929 Patent was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious. *See supra* § XII.O; *see also* Trial Tr. at 1778:9–13, 1782:21–1783:8 (Toth Direct). While Claim 1 of the '929 Patent does not include a limitation that the claimed method not substantially increase LDL-C, the expectation that highly purified EPA would produce large LDL-C increases in individuals with severe hypertriglyceridemia remains relevant to the analysis, because the purported motivation that Defendants offer as a reason to modify Lovaza to use high purity EPA with substantially no DHA is avoiding substantial increases in LDL-C. *See supra* ¶ 499. But because a person of ordinary skill would not have reasonably expected that high purity EPA would reduce triglycerides without substantially increasing LDL-C in persons with TG levels of at least 500 mg/dL, there could have been no such motivation. In addition, a person of ordinary skill would not have wanted to use a method requiring at least 96% EPA and substantially no DHA, for the additional reason that DHA was understood to have therapeutic advantages that a person of ordinary skill in the art would not have wanted to forego.

901. For all of these reasons, Claim 1 of the '929 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

X. Claim 5 of the '929 Patent Was Not Obvious

902. Claim 5 of the '929 Patent incorporates the elements of Claim 1 of the '929 Patent, but further specifies that the claimed method is effective to reduce apo B in subjects who have fasting triglyceride levels of at least 500 mg/dL. *See* PX 31 ('929 Patent) at 23. As with Claim 1 of the '929 Patent, Defendants contend that Claim 5 of the '929 Patent would have been obvious over Lovaza PDR, Mori 2000, Hayashi, and Kurabayashi. *See* Trial Tr. 828:10–22 (Heinecke Cross).

903. Claim 5 of the '929 Patent was not obvious for the same reasons that Claim 1 of the '929 Patent was not obvious (which, in turn, was not obvious for the same reasons that Claim 1 of the '728 Patent was not obvious). *See supra* §§ XII.O, XII.W; *see also* Trial Tr. 1778:9–13, 1782:21–1783:8 (Toth Direct).

904. In addition, for the same reasons as discussed above in connection with Claim 14 of the '715 Patent, it was not obvious to administer 4 g of high purity EPA (at least 96% by weight of all fatty acids present) and substantially no DHA to reduce apo B. *See supra* ¶¶ 870–72; *see also* Trial Tr. 1778:9–1780:22 (Toth Direct). As noted above, a person of ordinary skill in the art would have based her expectation about the effect of high purity EPA on the experience with Lovaza—the only FDA-approved omega-3 fatty acid treatment for severe hypertriglyceridemia—which did not show a reduction in apo B in persons with very high TGs. *See supra* ¶¶ 659–63, 719. Nor would a person of ordinary skill have understood that DHA was responsible for increasing apo B.

905. For all of these reasons, Claim 5 of the '929 Patent would not have been obvious to a person of ordinary skill in the art in March 2008.

XIII. REMEDIES

A. Defendants Should Be Enjoined From Marketing Their Approved Products Until Expiration of the Asserted Patents

906. Plaintiffs are entitled to a permanent injunction enjoining Defendants and their officers, agents, servants, employees, parents, subsidiaries, divisions, affiliates, and those persons

in active concert or participation with any of them, from making, using, selling, offering to sell, or importing their ANDA Products, or inducing any such conduct, until after the expiration of the Asserted Patents, including any extensions and additional periods of exclusivity. *See, e.g.*, 35 U.S.C. § 271(e)(4); 35 U.S.C. § 283.

B. Under 35 U.S.C. § 271(e)(4), Approval of Defendants' ANDAs Should Not Be Made Effective Until Expiration of the Asserted Patents

907. Section 271 (e)(4) provides: "For an act of infringement described in paragraph (2)" the court ***shall*** "order the effective date of any approval of the drug . . . product involved in the infringement to be a date which is not earlier than the date of the expiration ***of the patent which has been infringed***." 35 U.S.C. § 271(e)(4)(A) (emphasis added).

908. This relief is not discretionary; the Court is ***required*** to stay FDA approval. *See Vanda*, 887 F.3d at 1138 ("[U]pon a finding of patent infringement under § 271(e)(2), the district court ***must*** order remedies in accordance with § 271(e)(4)" (emphasis added)).

XIV. CONCLUSION

909. The evidence established that the Asserted Claims are infringed and are not invalid as obvious. Therefore, Amarin is entitled to judgment in its favor.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I am an employee of McDonald Carano LLP and that on February 14, 2020, I electronically filed the foregoing **PLAINTIFFS' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** with the Clerk of the Court using the Court's CM/ECF system, which electronically served the attorneys of record set forth below.

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